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Cradle-to-gate life cycle inventory of vancomycin hydrochloride

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ABSTRACT

A life cycle analysis on the cradle-to-gate production of vancomycin hydrochloride, which begins at natural resource extraction and spans through factory (gate) production, not only shows all inputs, outputs, and energy usage to manufacture the product and all related supply chain chemicals, but can highlight where process changes would have the greatest impact on raw material and energy consumption and emissions. Vancomycin hydrochloride is produced by a low-yield fermentation process that accounts for 47% of the total cradle-to-gate energy. The fermentation step consumes the most raw materials and energy cradle-to-gate. Over 75% of the total cradle-to-gate energy consumption is due to steam use; sterilization within fermentation is the largest user of steam. Aeration and agitation in the fermentation vessels use 65% of the cradle-to-gate electrical energy. To reduce raw materials, energy consumption, and the associated environmental footprint of producing vancomycin hydrochloride, other sterilization methods, fermentation media, nutrient sources, or synthetic manufacture should be investigated. The reported vancomycin hydrochloride life cycle inventory is a part of a larger life cycle study of the environmental consequences of the introduction of biocide-coated medical textiles for the prevention of MRSA (methicillin-resistant *Staphylococcus aureus*) nosocomial infections.

1. Introduction

Vancomycin hydrochloride, also referred to as vancomycin (Fig. 1), is a glycopeptide antibiotic used to treat resistant infections such as methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin is active against gram-positive bacteria and gram-negative cocci by inhibiting bacterial cell wall peptidoglycan synthesis (McCormick et al., 1955). Vancomycin was first isolated in 1956 by Eli Lilly, and it was referred to as Mississippi Mud due to the brown color from fermentation impurities. After the 1980s, purification methods improved, and the crystals were a pure white solid. Vancomycin is currently produced in low-yield by aerobic fermentation using *Amycolatopsis orientalis*.

The cradle-to-gate (ctg) life cycle inventory (LCI) for vancomycin hydrochloride presented here was performed as part of a larger life cycle inventory investigating the environmental footprint of treating a nosocomial MRSA infection. Vancomycin hydrochloride is also the third pharmaceutical active ingredient done by this research group. The synthetic production of sertraline hydrochloride and paroxetine were preciously investigated, and the LCI showed solvent and energy usage to have the greatest impacts on the life cycle assessment (Jimenez-Gonzalez and Overcash, 2000). This finding has led to the development of tools to help scientist select "greener" solvents for pharmaceutical manufacturing (Constable et al., 2007; Curzons et al., 2007; Jiménez-González et al., 2005; Slater and Savelski, 2007).

A life cycle assessment (LCA) is a "methodological framework for estimating and assessing the environmental impacts attributable to the life cycle of a product." (Hendrickson et al., 2006) ISO 14040 outlines the requirements for conducting life cycle inventory and assessment studies (International Standard Organization, 2006). The backbone of the LCA is the life cycle inventory, or a compilation of all inputs, outputs, and energy use of a product from resource extraction, manufacture, product use, recycling, and disposal (Rebitzer et al., 2004). A life cycle inventory gives the complete environmental picture of a product, and can be used to improve the manufacture of a product by highlighting where changes can be made to make the most impact on raw material and energy usage and emissions.

2. Goal and scope of the study

The intent of this work is to perform the cradle-to-gate inventory for production of vancomycin hydrochloride (vancomycin HCl) as part of a larger life cycle inventory investigating the environmental footprint of treating a nosocomial MRSA infection. An additional goal is to provide the life cycle community with usable process information for other future life cycle studies. The scope is from the natural resources through the manufacture of the active pharmaceutical ingredient (API) vancomycin hydrochloride (cradle-to-gate). Since this work is part of a larger life cycle inventory for treating a nosocomial infection, use and disposal of the API are not included in this LCI analysis.

In this study, transparent gate-to-gate (within the factory) inventories are used, and the cradle-to-gate inventory is the summation

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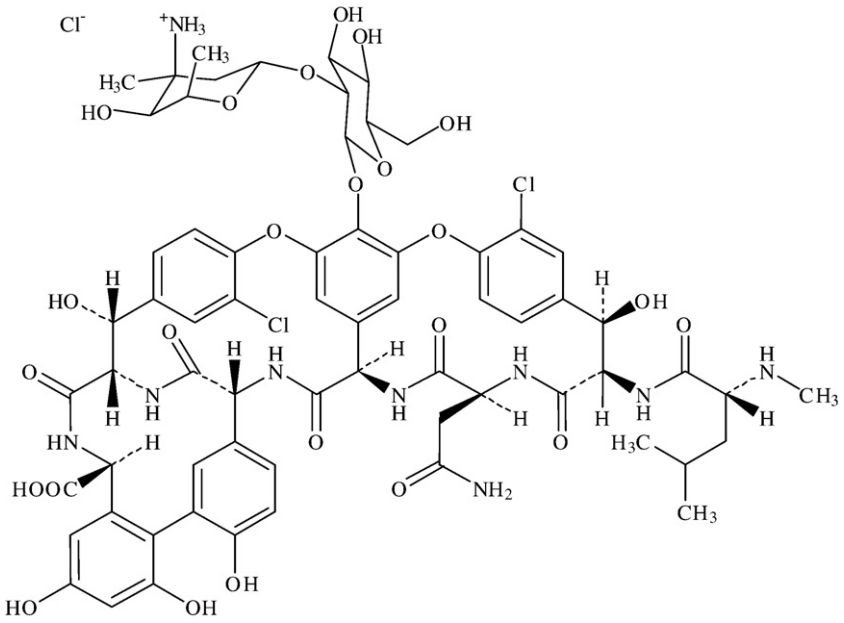

Fig. 1. Chemical structure of vancomycin hydrochloride.

of these first level inventories of each chemical in the supply chain. The functional unit, or basis of all analysis, is 1000 kg vancomycin hydrochloride crystals.

3. Methodology

The design-based LCI methodology (Jimenez-Gonzalez, 2000) using process flow diagrams and engineering design principles is used to collect inventory data (e.g., process inputs, process operations, waste generated, etc.) and complete gate-to-gate inventories for each chemical in the supply chain of the API. After selecting a generic manufacturing process and creating a flow diagram for each chemical input, the mass and energy balances are created to get the total raw materials input, energy consumption, and waste generated. Every life cycle inventory (LCI) follows a similar procedure, like an experiment in a laboratory. Information is gathered from articles, books, patents, company websites, and consultations with experts in the field, and then used with established process design heuristics to arrive at the LCI results. Once each gate-to-gate inventory is completed, a technical peer expert in the field reviews it, and changes are made as needed. Inventory data for vancomycin and all chemicals and solvents used in the manufacture of vancomycin have been produced by the authors using the process design method. In this process design method, waste management is not included as manufacturing information did not include waste treatment data. This information can be calculated in the future using the methodology outlined by Jimenez-Gonzalez et al. (Jimenez-Gonzalez et al., 2001) When allocation cannot be avoided by system boundary expansion, mass allocation is used.

For the gate-to-gate inventory of vancomycin, aerobic fermentation using *Amycolatopsis orientalis* (formerly *Nocardia orientalis* and *Streptomyces orientalis*) is the general manufacturing process selected, and a simplified process flow diagram is shown in Fig. 2. Although a variety of nutrient sources can be used (Jung et al., 2007), this inventory uses glucose (dextrose) and soy flour for fermentation as they are industrially available sources of complex nutrients and due to the availability of life cycle data previously studied by this research group. *A. orientalis* spores are transferred to flasks to inoculate starter nutrient medium, and incubated for 2 days. Fresh nutrient broth consisting of dextrose and soy flour as carbon and nitrogen sources, respectively, is added to Fermentor 1 and sterilized with steam for 15 min at 120 °C. Inoculum from the flask is then added to the cooled reactor medium and allowed to ferment for 24 h at 30 °C as air is sparged into the vessel. Fresh nutrient broth is then added to progressively larger bioreactors (Fermentors 2 and 3) and sterilized before the contents of the smaller bioreactors are added. The fermentation is four to six days. Air is added at a rate of 0.4 to 0.8 volumes of air per volume broth per minute, and the temperature is held at 30 °C (Cinar et al., 2003).

The fermentation broth, containing from 4 to 11 g Vancomycin/L broth (Jung et al., 2007), is filtered and passed through two adsorbers (Adsorbers 1 and 2) using Dowex 50 and Amberlite XAD-16 resins to separate the active ingredient vancomycin B and to decolorize and remove impurities. The solution is concentrated in an evaporator (E1). To further purify, vancomycin hydrochloride is then crystallized (in Crystallizer 1) using ammonium chloride, converted to the base vancomycin using urea (in R5), and crystallized again as vancomycin hydrochloride using ammonium chloride (in Crystallizer 2). The vancomycin hydrochloride crystals are filtered and dried.

To calculate the energy used, it is assumed that 25% of the glucose is converted to vancomycin, according to the reaction mechanism of Dunstan et al (Dunstan et al., 2000) showing 24 mol of glucose are converted to 1 mol of vancomycin, while 75% is converted to exothermic energy by glycolysis (McIntyre et al., 1996). The fermentation energy (used to calculate cooling water requirements) is calculated from the heats of reaction for the dextrose glycolysis and dextrose-to-vancomycin reactions.

4. Inventory results

The chemical tree in Fig. 3 is a condensed version of the full vancomycin hydrochloride chemical tree. The full tree includes all of the chemicals in the supply chain of the final product. To abbreviate the chemical tree, only the first two levels are shown, along with the number of chemicals that went into the production of the second level chemicals. The natural resources are on the far right. For example, twenty-eight chemicals are in the ctg supply chain to manufacture dextrose. This number includes duplicates, as a chemical input may be used to manufacture more than one chemical product. This life cycle inventory included thirty-eight different chemicals and the gate-to-gate inventories that were performed for each of these chemicals. Chemical inputs that were less than 5% (by mass) of the final product