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Environmental resource footprinting of drug manufacturing: Effects of scale-up and tablet dosage

Wouter De Soete[a,*], Lieselot Boone[a], Filip Willemse[b], Erik De Meyer[b], Bert Heirman[b], Herman Van Langenhove[a], Jo Dewulf[a]

[a] Research Group Environmental Chemistry and Technology (ENVOC), Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium[1]

[b] Johnson & Johnson PRD, Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse, Belgium[2]

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ABSTRACT

The formulation and scale-up of batch processes is one of the major challenges in the development of pharmaceutical dosage forms and at the same time a significant resource demanding process which is generally overlooked in environmental sustainability assessments. First, this paper proposes general trends in the experience curve of cumulative resource consumption of pharmaceutical tablet manufacturing of PREZISTA® 800 mg through wet granulation (WG) at four consecutive scales in both R&D and manufacturing environments (resp. WG1 = 1 kg/h, WG5 = 5 kg/h, WG30 = 30 kg/h and WG240 = 240 kg/h). Second, the authors aim at evaluating the environmental impact from a life cycle perspective of a daily consumption of PREZISTA® 2× 400 mg tablets versus the bioequivalent PREZISTA® 800 mg tablet which was launched to enhance patient compliance. Environmental sustainability assessment was conducted at three different system boundaries, which enables identification, localization and eventually reduction of burdens, in this case natural resource extraction. Exergy Analysis (EA) was used at process level (α) and plant level (β) while a cradle-to-gate Exergetic Life Cycle Assessment (ELCA) was conducted at the overall industrial level (γ) by means of the CEENE method (Cumulative Exergy Extraction from the Natural Environment). Life cycle stages taken into account are Active Pharmaceutical Ingredient (API) production, Drug Product (DP) production and Packaging. At process level (α), the total resource extraction for the manufacturing of one daily dose of PREZISTA® (800 mg tablet) amounted up to 0.44 MJ_{ex} at the smallest scale (WG1) while this amount proved to be reduced by 58%, 79% and 83% at WG5, WG30 and WG240 respectively. Expanding the boundaries to the overall industrial level (γ) reveals that the main resource demand is at the production of the Active Pharmaceutical Ingredient (API), excipients, packaging materials and cleaning media used in DP production. At the largest scale (WG240) the use of cleaning media during DP production contributes considerably less to the total resource extraction. Overall, the effect of scale-up and learning on resource consumption during DP production showed to possess a power-law experience curve $y = 2.40 * x^{-0.57}$ when shifting from WG1 (smallest lab scale) to WG240 (industrial manufacturing). Tablet dosage (2× 400 mg versus 1× 800 mg) did not significantly affect the absolute environmental burden. However, the relative contribution of resource categories did change due to the different production technology. It could be concluded that in meeting social and economic demands by launching the PREZISTA® 800 mg tablet, no trade-off in environmental burden occurred. On the long term, future research should strive to take into account R&D processes and all services related to pipeline activities taking place prior to market launch and eventually to allocate impacts to the final product.

1. Introduction

In the chemical and pharmaceutical industry, both companies and research institutes have been developing metrics and tools to assess and manage the 'greenness' of their products and services throughout the last decades. A distinction is made between process-oriented indicators (e.g. E factor, Process Mass Intensity, etc.) and life cycle oriented eco-indicators (e.g. Carbon Footprint)

* Corresponding author.
E-mail addresses: Wouter.DeSoete@UGent.be, wouterdesoete@gmail.com (W. De Soete), BHEIRMAN@its.jnj.com (B. Heirman).
[1] Tel.: +32 9264 5948; fax: +32 9264 6243.
[2] Tel: +32 1460 6347.

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Nomenclature

ACS	American Chemical Society
API	Active Pharmaceutical Ingredient
α	process level
BOM	Bill of Materials
β	plant level
CEENE	Cumulative Exergy Extracted from the Natural Environment
CIP	Cleaning in Place
c_p	isobaric specific heat capacity
DC	Direct Compression
DP	Drug Product
EA	Exergy Analysis
ELCA	Exergetic Life Cycle Assessment
ex^{PH}	physical exergy
FU	functional unit
GCI	Green Chemistry Institute
GCIPR	Green Chemistry Institute Pharmaceutical Roundtable
HIV	Human Immunodeficiency Virus
γ	overall industrial level
H	enthalpy of stream
H_0	enthalpy of reference state
ILCD	International Reference Life Cycle Data System
LCA	Life Cycle Assessment
LCI	Life Cycle Inventory
LCIA	Life Cycle Impact Assessment
MSDS	Material Safety Data Sheet
P&ID	Piping & Instrumentation Diagram
p	pressure of system
p_0	pressure of reference state
R	universal gas constant
S	entropy of stream
S_0	entropy of reference state
T	temperature of system
T_0	temperature of reference state
WG	wet granulation

(Jimenez-Gonzalez et al., 2013; Lapkin and Constable, 2009). With reference to green chemistry and green engineering, process indicators are traditionally used to assess and eventually enhance the environmental sustainability of products and processes; however, a life cycle approach is favoured to avoid outsourcing of burdens (Dewulf et al., 2007b). The latter includes the cumulative environmental burden exerted through all steps of the supply chain – and more generally the life cycle – of a certain product or service, including both upstream and downstream processing, ranging from raw material extraction to the end of life waste treatment (Azapagic, 1999; Russell et al., 2005). Next to the development and profound elaboration of assessment methods with respect to the pharmaceutical industry, some fast assessment tools were developed to estimate the environmental sustainability of Active Pharmaceutical Ingredient (API) production processes (Curzons et al., 2007; Wernet et al., 2009). These generic tools, typically circumventing the need for an in-depth process analysis, rely on empirical models built on rather scarce confidential data. A more detailed, less generic model was developed at Ghent University in order to evaluate the integrated resource consumption of a multipurpose pharmaceutical production plant of the Janssen Group, Johnson & Johnson Family of Companies (Van der Vorst et al., 2009, 2011). Taking into account the Drug Product (DP) production process (pharmaceutical production step in which the API is formulated in combination with various excipients in a so-called dosage form), the American Chemical Society (ACS) Green Chemistry Initiative Pharmaceutical Roundtable (GCIPR) developed a simplified, mass accounting fast Life Cycle Assessment (LCA) tool (Jimenez-Gonzalez et al., 2013).

With aforementioned assessment tools, an important step was taken towards generic environmental sustainability assessments of pharmaceuticals. However, these tools do not yet account for the early and late development stages of a pharmaceutical drug product, which typically comprise around 14 out of 20 years of the patent term (Ellery and Hansen, 2012; Rees, 2011). Moreover, they cannot predict future environmental impacts at industrial scale when the pharmaceutical is at an early development stage. This forecasting perspective should be embedded in a tool aiming at the provision of eco-indicators intended for integration in R&D decision trees (De Soete et al., 2013). This way, one can anticipate on the environmental burden of first generation medicines by including eco-indicators as criterion for decision-making at important development stages, next to drug bio-availability, patient compliance, cost-effectiveness, etc. The predictive impact assessment can be accomplished through evaluation of environmental burdens of production technologies at different production scales (e.g. lab scale, clinical production scale, pilot scale, industrial manufacturing scale). Note that in other sectors (e.g. the energy sector) power-law relationships were already established in order to predict e.g. the fuel consumption and costs of energy conversion technologies (Caduff et al., 2010, 2012).

The objective of this research paper is twofold. First of all, it analyses cumulative resource consumption of pharmaceutical tablet manufacturing of PREZISTA® 800 mg through wet granulation (WG) at four consecutive scales (resp. WG1 = 1 kg/h, WG5 = 5 kg/h, WG30 = 30 kg/h and WG240 = 240 kg/h) and proposes the experience curve (Comparative analysis 1, Fig. 1). PREZISTA® is a well-known second-generation protease inhibitor used to slow down Human Immunodeficiency Virus (HIV) infections. This typically high weight tablet requires wet granulation by capillary and viscous forces to enhance the flowability of the powder mix and finally its tablet properties (Franch-Lage et al., 2011). Second, this study evaluates the environmental impact from a life cycle perspective of a daily consumption of PREZISTA® 2× 400 mg versus the bioequivalent 800 mg which was launched to enhance patient compliance (Comparative analysis 2). This tablet allows patients to take only one tablet once a day instead of taking two 400 mg tablets per day. In contrast to the PREZISTA® 800 mg tablet, production of the PREZISTA® 400 mg tablet covers Direct Compression (DC) of the powder mix, yielding good tablet properties as presented in Fig. 1. Environmental sustainability assessment in this study was conducted at three different system boundaries, which enables identification, localization and eventually reduction of environmental burdens, in this case resource extraction. Exergy Analysis (EA) was used at process level (α) and plant level (β) while a cradle-to-gate Exergetic Life Cycle Assessment (ELCA) was conducted at the overall industrial level (γ) (Dewulf et al., 2007a, 2008). Life cycle stages taken into account are API production, DP production and Packaging (Fig. 1).

2. Methodology

In pursuit of harmonisation in reporting methodology of a Life Cycle Assessment (LCA), the following paragraphs briefly elaborate the chosen methodological framework according to the ILCD Handbook Guidelines (European Commission – Joint Research Centre – Institute for Environment and Sustainability, 2010).