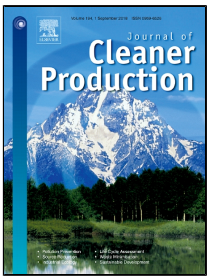
# Accepted Manuscript




Waste generation, product yield evaluation and exergy analysis during bisphosphonate synthesis and medical drug production processes

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| PII: | S0959-6526(18)31966-8 |
| DOI: | 10.1016/j.jclepro.2018.06.307 |
| Reference: | JCLP 13453 |
| To appear in: | *Journal of Cleaner Production* |
| Received Date: | 24 October 2017 |
| Accepted Date: | 30 June 2018 |

Please cite this article as: Banu Yavuztürk, Seyda Bucak, Mustafa Özilgen, Waste generation, product yield evaluation and exergy analysis during bisphosphonate synthesis and medical drug production processes, *Journal of Cleaner Production* (2018), doi: 10.1016/j.jclepro.2018.06.307

# Waste generation, product yield evaluation and exergy analysis during bisphosphonate synthesis and medical drug production processes

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## Abstract

Introduction of the waste of the pharmaceutical industry to the biosphere creates unusual potential disease patterns. Achieving the active pharmaceutical ingredient (API) production by utilizing the minimum energy and generating as little waste as possible are among the reasonable cleaner production practices. Zoledronic acid is the API of some bone-disease drugs. It is synthesized via the reaction of 1h-imidazole-1-yl- acetic acid hydrochloride with phosphorous acid and phosphorous halogen at moderate temperatures. The product is later separated by crystallization in water. Since the concentration of API is very low in the finished product, generally 50 g of API satisfies the annual market demand. Chemical processes are generally investigated to determine the most convenient production procedures and equipment. In the studies performed in small scale set up, it is important to foresee an upscale design. Exergy utilization is among the considerations in process design and there is almost no information available in the literature yet, regarding the exergy analysis of the production processes of pharmaceuticals.

"*Cradle to grave*" exergy analyses, beginning with the raw materials and ending with retail packaging of a pharmaceutical product is studied here by referring to bisphosphonate production. Although the synthesis stage of this study refers to the production of a single API, the packaging stage of the process refers to the entire pharmaceutical industry, where similar practices are employed.

During the chemical synthesis of zoledronic acid under GMP (good manufacturing practice) conditions, the most energy consuming step was found to be crystallization. On the other hand, the most energy consuming step during sterile finished product manufacturing was filling, followed by sterilization of the primary packaging equipment and the materials, and the operation of the HVAC system. The initial cumulative degree of perfection (CDP) was calculated to be $1.47 \times 10^{-2}$ % for the API synthesis, however exergy efficiency of the synthesis process to $2.29 \times 10^{-2}$ % with increasing the yield through process optimization. The CDP of the finished product was 17 % and 75 % before and after packaging of the finished product, respectively. Synthesis at the maximum attainable conversion ratio and the highest exergy efficiency assures minimum waste generation.