Using Aspen Plus to Simulate Pharmaceutical Processes – An Aspirin Case Study

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Abstract

The use of chemical process simulators such as Aspen Plus for pharmaceutical applications has received relatively little attention. This is due, in part, to the specialized raw materials, products and unit operations that are involved in the processes. This paper illustrates that the Aspen Plus simulation system has many of the functional capabilities that make it an attractive tool for simulating pharmaceutical processes. These features include solids handling capabilities, batch processing, drying, process optimization including data reconciliation and parameter estimation, and finally cost estimation including capital and operating costs. These features are demonstrated using a process to manufacture the common over-the-counter pharmaceutical commonly referred to by its trade name, aspirin. Aspirin also known as ASA or acetylsalicylic acid is one of the oldest pharmaceuticals in wide spread use today and it is relatively simple to manufacture. However, the simulation of the process using traditional chemical process simulators is not straightforward and exhibit several difficulties involved in solids handling and batch processing. The synthesis of ASA is based on the acetylation of salicylic acid with acetic anhydride:

$$C_7H_6O_3 + C_4H_6O_3 \rightarrow C_9H_8O_4 + CH_3COOH$$
$$\text{salicylic acid} + \text{acetic anhydride} \rightarrow \text{acetylsalicylic acid} + \text{acetic acid}$$

The reactants (salicylic acid and acetic anhydride) are mixed together with a small amount of sulphuric acid (H_2SO_4) acting as a catalyst. The mixture is then heated to about 50 °C to increase the reaction kinetics. The liquid mixture of unreacted salicylic acid and acetic anhydride along with acetylsalicylic acid and acetic acid products are then fed into a crystallizer operated about 3 °C. The objective of the crystallizer is to precipitate dissolved ASA into solid ASA by cooling the solution below the solubility limit. A hydro-cyclone is then employed to separate the solid ASA from the solid-liquid stream by spinning the mixture at high velocity. The cyclone separates the solid ASA from the solid-liquid stream while allowing about 15 % of the supernatant liquid to remain with the solid stream. The solid ASA plus supernatant stream are finally dried to ~ 17 wt.% moisture (dry basis) which is typical in ASA dryers.

Aspen Plus was used to simulate a process designed to produce 145 kg/h of ASA. Based on this case study it was found that this process was able to convert about 78 wt.% of the reactants to ASA product at a production cost of approximately $3/kg. Based on this preliminary feasible process, process improvements in the form of optimization and process control were undertaken including studying the effect of the reactor temperature and recycle split fraction on the process operation and economics. Heat exchanger network synthesis and the production rate were also investigated.

Keywords
Process Simulation, Pharmaceuticals, Aspen Plus, Aspirin Production, Economic Analysis.

Biographies

Alisa Douglas is a fourth year iBioMed co-op student at McMaster University in Hamilton, Ontario. The iBioMed program (Integrated Biomedical Engineering and Health Sciences) is an interdisciplinary program that combines core courses in the Health Sciences program with core courses in an Engineering discipline (chemical engineering in her case). The resulting five-year program contains a rich blend of mathematics, science, engineering science and health science integrated with design courses each year. She has already completed courses in Anatomy, Cellular Biology, Biochemistry, Epidemiology, Biomedical Signals & Systems, Numerical Methods, Transport Processes, Reactor Design, and Process Synthesis and Simulation. She has completed three team-based design courses each involving hands-on sensor development. She has also completed co-op work terms at King Mongkut's University of Technology Thonburi (Bangkok, Thailand), University of Waterloo and McMaster University.

Ali Elkamel is a professor of Chemical Engineering at the University of Waterloo and a registered Professional Engineer in the Province of Ontario. He holds a B.S. in Chemical Engineering and a B.S. in Mathematics from Colorado School of Mines, an M.S. in Chemical Engineering from the University of Colorado-Boulder, and a PhD in Chemical Engineering from Purdue University – West Lafayette, Indiana. His specific research interests are in computer-aided modeling, optimization, and simulation with applications to energy production planning, pollution prevention, and product design. In essence, the underpinning focus of his research efforts have been on promoting sustainable development via the application of systems engineering and mathematical optimization techniques. He is also interested in incorporating the systems approach in engineering education. He has been funded for numerous research projects from government and industry. His research output includes over 365 journal articles and 35 book chapters. He is also a co-author of five books. Two recent books were published by Wiley and entitled "Planning of Refinery and Petrochemical Operations" and "Environmentally Conscious Fossil Energy Production".