OPTIMIZE MANUFACTURING OF PHARMACEUTICAL PRODUCTS WITH PROCESS SIMULATION AND PRODUCTION SCHEDULING TOOLS

V. Papavasileiou, A. Koulouris, C. Siletti and D. Petrides*

Abstract: This article describes how batch process simulators and scheduling tools can be used to facilitate and expedite development and commercialization of pharmaceutical products.

Keywords: pharmaceutical manufacturing; process simulation; computer-aided process modelling; production scheduling; cost analysis; cycle time reduction; risk assessment; Monte Carlo simulation; lean manufacturing.

**Correspondence to:* Dr D. Petrides, Intelligen, Inc., 2326 Morse Avenue, Scotch Plains, New Jersey, USA.
E-mail: dpetrides@intelligen.com

DOI: 10.1205/cherd06240

0263–8762/07/ $30.00 + 0.00

Chemical Engineering Research and Design

Trans IChemE, Part A, July 2007

INTRODUCTION

The global competition in the pharmaceutical industry and the increasing demands by governments and citizens for affordable medicines has focused the industry's attention on manufacturing efficiency. In this new era, improvements in process and product development approaches and streamlining of manufacturing operations can have a profound impact on the bottomline. Process simulation and scheduling tools can play an important role in this endeavor. The role of such tools in the development and manufacturing of active pharmaceutical ingredients (APIs) has been reviewed in the past (Petrides *et al.*, 1996, 2002a, b; Petrides and Siletti, 2004; Thomas, 2003; Hwang, 1997; Harrison *et al.*, 2003; Tan *et al.*, 2006). The focus of this article is on the role of such tools in the development and manufacturing of pharmaceutical products.

Common forms of pharmaceutical products include tablets, capsules, ointments, creams, solutions in syringes and vials. Their preparation involves mixing of the active ingredient(s) with various excipients that increase the shelf-life of the product and facilitate the delivery of the active ingredient. Manufacturing of inject able products involves filling of syringes or vials under aseptic conditions.

During process development, process simulation software is used to perform the following tasks:

- represent the entire process on the computer;
- perform material and energy balances;
- estimate the size of equipment;
- calculate demand for utilities as a function of time;
- estimate the cycle time of the process;
- perform cost analysis;
- asses the environmental impact, and so on.

The availability of a good model on the computer improves the understanding of the entire process by the team members and facilitates communication. What-if and sensitivity analyses are greatly facilitated by such tools. The objective of such studies is to evaluate the impact of critical parameters on various key performance indicators (KPIs), such as production cost, cycle times and plant throughput. If there is uncertainty for certain input parameters, sensitivity analysis can be supplemented with Monte Carlo simulation to quantify the impact of uncertainty. Cost analysis, especially capital cost estimation, facilitates decisions related to in-house manufacturing versus outsourcing. Estimation of the cost-of-goods identifies the expensive processing steps and such information is used to guide R&D work in a judicious way.

When a process is ready to move from development to manufacturing, process simulation facilitates technology transfer and process fitting. A detailed computer model provides a thorough description of a process in a way that can be readily understood and adjusted by the recipients. Process adjustments are commonly required when a new process is moved into an existing facility whose equipment is not ideally sized for the new process. The simulation model is used to adjust batch sizes, figure out cycling of certain steps (for equipment that cannot handle a batch in one cycle), estimate recipe cycle times, and so on.

Production scheduling tools play an important role in manufacturing (large scale as well as clinical). They are used to generate production schedules on an on-going basis in a way that does not violate constraints related to the limited availability of equipment, labor resources, utilities, inventories of materials, and so on. Production scheduling tools close the gap between ERP/MRP II tools and the plant floor (Plenert and Kirchmier, 2000). Production schedules generated by ERP (Enterprise Resource Planning) and MRPII (Manufacturing Resource Planning) tools are typically based on coarse process representations and approximate plant capacities and, as a result, solutions generated by these tools may not be feasible, especially for multi-product facilities that operate at high capacity utilization. That often leads to late orders that require expediting and/or to large inventories in order to maintain customer responsiveness. 'Lean manufacturing' principles, such as just-in-time production, low work-in-progress (WIP), and low product inventories cannot be implemented without good production scheduling tools that can accurately estimate capacity.

COMMERCIALLY AVAILABLE SIMULATION AND SCHEDULING TOOLS

Process simulation programs, also known as process simulators, have been in use in the chemical and petrochemical industries since the early 1960s. Established simulators for those industries include: Aspen Plus and HYSYS from Aspen Technology, Inc. (Cambridge, MA), ChemCAD from Chemstations, Inc. (Houston, TX), and PRO/II from SimSci-Esscor, Inc. (Lake Forest, CA).

The above simulators have been designed to model primarily continuous processes and their transient behaviour for process control purposes. Most pharmaceutical products, however, are produced in batch and semi-continuous mode. Such processes are best modeled with batch process simulators that account for time-dependency and sequencing of events. Batches from Batch Process Technologies, Inc. (West Lafayette, IN) was the first simulator specific to batch processes. It was commercialized in the mid-1980s. All of its operation models are dynamic and simulation always involves integration of differential equations over a period of time. In the mid-1990s, Aspen Technology introduced Batch Plus, a recipe-driven simulator that targeted batch pharmaceutical processes. At around the same time, Intelligen, Inc. (Scotch Plains, NJ) introduced SuperPro Designer. The initial focus of SuperPro was on production of APIs (synthetic and biosynthetic) and specialty chemicals. Over the years its scope has been extended to include modeling of processes for the production of pharmaceutical and consumer products.

Discrete-event simulators have also found applications in the pharmaceutical industries, especially in modeling and debottlenecking of packaging operations. Established tools of this type include ProModel from ProModel Corporation (Orem, UT), Arena and Witness from Rockwell Automation, Inc. (Milwaukee, WI), Extend from Imagine That, Inc. (San Jose, CA), and FlexSim from FlexSim Software Products, Inc. (Orem, UT). The focus of models developed with such tools is usually on the minute-by-minute time-dependency of events and the animation of the process. Material balances, equipment sizing, and cost analysis tasks are usually out of the scope of such models. Some of these tools are quite customizable and third party companies occasionally use them as platforms to create industry-specific modules. For instance, BioPharm Services, Ltd. (Bucks, UK) have created a module with emphasis on biopharmaceutical processes that runs on top of Extend.

MS Excel from Microsoft is another common platform for creating models for pharmaceutical processes that focus on material balances, equipment sizing, and cost analysis. Some companies have even developed models in Excel that capture the time-dependency of batch processes. This is typically done by writing extensive code (in the form of macros and subroutines) in VBA (Visual Basic for Applications) that comes with Excel. K-TOPS from Alfa Laval Biokinetics, Inc. (Philadelphia, PA) belongs to this category.

In terms of production scheduling, established tools include Optiflex from i2 Technologies, Inc. (Irving, TX), SAP APO from SAP AG (Walldorf, Germany), ILOG Plant PowerOps from ILOG SA (Gentilly, France), Aspen SCM (formerly Aspen MIMI) from Aspen Technology, Inc. (Cambridge, MA), and so on. Their success in the pharmaceutical industry, however, has been rather limited so far. Their primary focus on discrete manufacturing (as opposed to batch chemical manufacturing) and their approach to scheduling from a mathematical optimization viewpoint are some of the reasons of the limited market penetration.

SchedulePro from Intelligen, Inc. (Scotch Plains, NJ) is a new finite capacity scheduling tool that focuses on scheduling of batch and semi-continuous chemical and related processes. It is a recipe driven tool with emphasis on generation of feasible solutions that can be readily improved by the user in an interactive manner.

Examples that illustrate the benefits from the use of simulation and scheduling tools in the production of pharmaceutical products follow.

MODELLING AND ANALYSIS OF A TABLET MANUFACTURING PROCESS

We will use a tablet manufacturing process as a representative example to demonstrate the use of process simulation and scheduling tools in the development and manufacturing of finished pharmaceutical products. To model an integrated process on the computer using SuperPro Designer, the user starts by developing a flowsheet that represents the overall process. Figure 1, for instance, displays part of the flowsheet of a tablet manufacturing process. The flowsheet is developed by putting together the required unit procedures (see next paragraph for explanation), and joining them with material flow streams. Next, the user initializes the flowsheet by registering the various materials that are used in the process and specifying operating conditions and performance parameters for the various operations.

Most pharmaceutical processes operate in batch or semi-continuous mode. This is in contrast to petrochemical and other industries that handle large throughputs and use continuous processes. In continuous operations, a piece of equipment performs the same action all the time. In batch processing, on the other hand, a piece of equipment goes through a cycle of operations. For instance, a Slurry Preparation step (P-1 in V-101) includes the following operations (see Figure 2): *Sanitize*, *Charge USP Water, Charge*