Computers and Chemical Engineering 42 (2012) 15–29

Contents lists available at SciVerse ScienceDirect

Computers and Chemical Engineering

journal homepage: www.elsevier.com/locate/compchemeng

A perspective on PSE in pharmaceutical process development and innovation

Krist V. Gernaey*, Albert E. Cervera-Padrell, John M. Woodley

Department of Chemical and Biochemical Engineering, Technical University of Denmark, Building 229, DK-2800 Kgs., Lyngby, Denmark

ARTICLE INFO

Article history:
Received 21 September 2011
Received in revised form 26 February 2012
Accepted 28 February 2012
Available online 8 March 2012

Keywords:
Continuous pharmaceutical manufacturing
Design space
PAT
Pharmaceutical production
Process development
Sustainability

ABSTRACT

The pharmaceutical industry is under growing pressure to increase efficiency, both in production and in process development. This paper discusses the central role of Process Systems Engineering (PSE) methods and tools in pharmaceutical process development and innovation, and searches for answers to questions such as: Which PSE methods can be applied readily? Where is more method development needed? The paper covers key subjects for development of economically and environmentally sustainable pharmaceutical processes, including Process Analytical Technology in its broadest sense, continuous pharmaceutical manufacturing and green processes, and is illustrated with a series of short examples taken from the literature and ongoing research projects.

1. Introduction

Today more than ever, the pharmaceutical industry is under pressure to deliver its end products cheaper, faster and more efficiently (Federsel, 2003). Competition from generic drug manufacturers is undoubtedly one of the main drivers, and has already triggered dramatic changes. Indeed, many of the traditional research-based pharmaceutical companies have started the production of generic drugs during the past five years, and are thus in direct competition with generic drug manufacturers. Such competition demands particular focus on production cost. In addition, there is – in particular in Europe – a growing consumer demand for so called 'green' pharmaceutical products (i.e. the introduction of greener, more environmentally friendly production methods to manufacture pharmaceuticals). The latter demand originates from a growing awareness that drug manufacturing processes have a significant environmental impact (Sheldon, 1992, 2007).

In this paper, the focus is on production of small-molecule (MW < 1000) drug substances – active pharmaceutical ingredients (APIs), new chemical entities (NCEs) – that are produced via organic synthesis. A generic process flowsheet of a small-molecule API production process is provided in Fig. 1. Aside from antibiotics, which are small molecules that for many decades have been produced by fermentation, there is an emerging trend toward bio-production methods (such as enzyme-based catalysis). Interestingly, several principles and concepts that will be highlighted in the manuscript can also be applied to large-molecular (MW > 1000), biotechnology-based drug substances – also called biopharmaceuticals – which includes for example monoclonal antibodies and therapeutic proteins.

Traditionally, the pharmaceutical industry has been rather reluctant to introduce innovative methods in its production processes, despite the fact that the cost for the development of a new drug continually increases, while the patent life time is fixed (Federsel, 2003). Considering the typical development cycle of a drug, two obvious ways of increasing profit are: (1) more rapid process development, and thus maximization of the time between product release and patent expiration; and (2) streamlining the full-scale production system to reduce production costs, such that traditional research-based drug manufacturers can also compete with generic drug manufacturers when the patent of a drug has expired. In both cases, we are convinced that increased and systematic use of Process Systems Engineering (PSE) methods (Klatt & Marquardt, 2009; Stephanopoulos & Reklaitis, 2011) can be advantageous. In this context, the introduction of the Process Analytical Technology (PAT) guidance by the FDA (2004) is an important milestone as well, since its publication has ended a long period of

Abbreviations: ANN, artificial neural network; API, active pharmaceutical ingredient; CAMD, computer-aided molecular design; CFD, computational fluid dynamics; CP, continuous processing; CPM, continuous pharmaceutical manufacturing; CPP, critical process parameter; CQA, critical quality attribute; DEM, discrete element method; DoE, design of experiments; FEM, finite element method; iPLS, interval PLS; LCA, life cycle assessment; LLE, liquid–liquid extraction; MSPC, multivariate statistical process control; MW, molecular weight; NCE, new chemical entity; NIR, near infra-red; OED, optimal experimental design; PAT, Process Analytical Technology; PBM, population balance model; PCA, Principal Component Analysis; PDE, partial differential equation; PLS, Partial Least Squares; PMI, process mass intensity; PSE, Process Systems Engineering; QbD, quality by design.

* Corresponding author. Tel.: +45 45252970; fax: +45 45932906.
E-mail address: kvg@kt.dtu.dk (K.V. Gernaey).

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doi:10.1016/j.compchemeng.2012.02.022

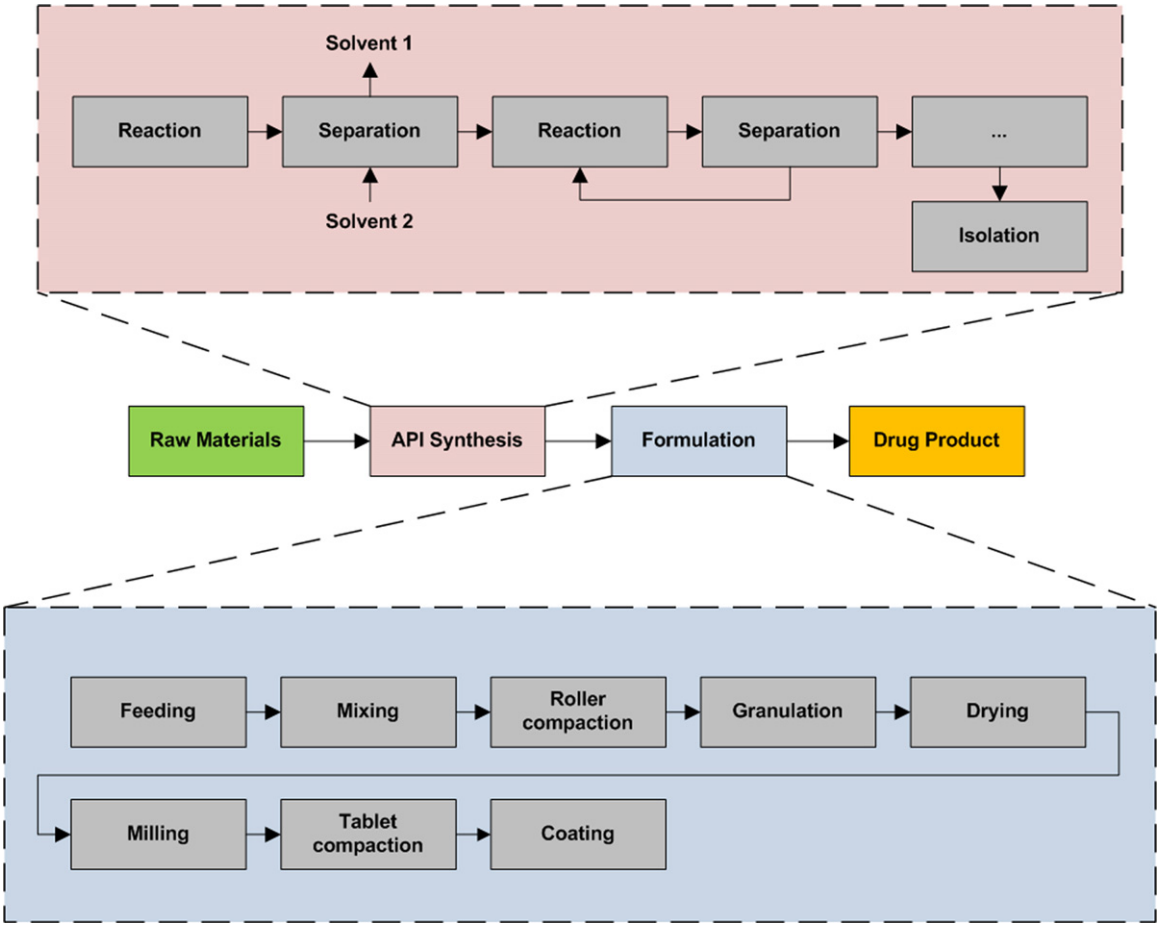

Fig. 1. Typical flowsheet for a pharmaceutical manufacturing process. PSE methods and tools can be used to obtain data, analyze, model, simulate, control and optimize each unit operation. Detailed information about specific unit operations for the formulation part of the process is provided elsewhere (feeding: Boukouvala et al., 2010; mixing/blending: Boukouvala et al., 2010; roller compaction: am Ende et al., 2007; granulation: Vervaet & Remon, 2005; drying: Mortier et al., 2011; milling: Bilgili & Scarlett, 2005; tablet compaction: Michaut et al., 2010; coating: Prpich et al., 2010).

regulatory uncertainty. Indeed, the PAT guidance makes clear that regulatory bodies are in favor of more efficient production methods, as long as a safe (in-specification) product can be guaranteed. The disappearance of such regulatory uncertainty opens up new and exciting possibilities for innovation in pharmaceutical production processes, and thereby also increased need for PSE methods and tools.

This paper will provide a perspective on the use of PSE methods in pharmaceutical process development and innovation. It searches for the answers to questions such as: Which PSE methods can be applied readily? Where is more method development needed? The paper will be illustrated with examples taken from the literature and ongoing research projects. Rather than providing a long list of PSE methods and tools along with potential applications of those methods, the manuscript has been structured according to a number of main topics which we think are of major importance today: implementation of PAT strategies, continuous production processes and green pharmaceutical processes. It is worth noting as well that a topic such as 'continuous production processes' was ranked as the top priority on the list of key green engineering research areas that has recently been published as a result of the brainstorming and prioritization exercises of the American Chemical Society (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable (Jiménez-González et al., 2011). This confirms that a more efficient process nearly always results in a greener process, and that PSE methods and tools can play a prominent role in paving the way toward more efficient and innovative pharmaceutical production processes for small molecules. Finally, in the discussion, we highlight several problems related to the application of PSE methods and tools in pharmaceutical process development and innovation, which also includes a short perspective on the function of PSE methods in the drug development cycle.

2. Process Analytical Technology (PAT)

Process Analytical Technology (PAT) (FDA, 2004) is undoubtedly one of the most influential new trends in pharmaceutical manufacturing in recent years. Interestingly, seen from the perspective of the PSE community, PAT does not really bring so much new, since the concepts described in the PAT guidance have been applied for quite a long time by several other industries (e.g. petrochemical, polymer and chemical sectors) (Kourti, 2006). As a consequence, there are quite a number of PSE methods and tools that can be used in a PAT context, resulting from developments that took place in other industries. Here, we will first introduce the most essential PAT terminology, then discuss the most important PSE tools that can be used for PAT, and afterwards shift focus to PAT implementation and especially the role that PSE plays in PAT implementation.

2.1. PAT terminology

Several new concepts were introduced in the PAT guidance (FDA, 2004). The most important ones are: