Computers and Chemical Engineering 60 (2014) 396–402

Contents lists available at ScienceDirect

Computers and Chemical Engineering

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

A computer aided optimal inventory selection system for continuous quality improvement in drug product manufacture

Salvador García Muñoz[a,*], Vionnette Padovani[b], Jose Mercado[b]

[a] Pfizer Worldwide Research & Development, Groton, CT 06340, USA
[b] Pfizer Global Manufacturing, Vega Baja 00693, Puerto Rico

ARTICLE INFO

Article history:
Received 23 July 2013
Received in revised form
16 September 2013
Accepted 25 September 2013
Available online 9 October 2013

Keywords:
Quality by design
Latent variable regression
Pharmaceutical drug product
Optimization
PLS
MINLP

ABSTRACT

The multivariate interaction of the raw materials' physical properties can be critical to the quality of the final drug product. Although an elegant solution to this problem is the establishment of multivariate specifications this becomes difficult (if not impossible) to implement when the interactions take place across materials that are sourced by different vendors. As an alternate solution, this work presents a feed-forward corollary approach to model predictive control (MPC) to improve the product quality from a lot-driven-operation; where there are no available manipulated variables (MV) in the process. In these special cases the only degree of freedom available to be used as a MV for control is the lot-to-lot variability in the raw materials. This work presents an extension to our earlier work (Ind. Eng. Chem. Res. 2013, 52 (17), pp. 5934–5942) to consider a horizon of n lots to be manufactured. By considering this horizon of future lots (rather than just the next one) our method allows the discretionary use of all materials to ensure that the quality of all the future n lots is within specification. This paper presents a detailed discussion of the objective function used and also reports the results of implementing this method to the manufacture of a pharmaceutical drug product in a commercial manufacturing setting.

1. Introduction

During the past decade the regulation of the pharmaceutical industry has transformed the strategies taken to ensure the quality of pharmaceutical products. Current guidance documents encourage practitioners to implement active (and pro-active) strategies to quality control rather than passive ones that rely solely on testing the final product (Food & Drug Administration, 2009; U.S. Dept. of Health & Human Services, 2003).

These trends, along with an increasing competitive business environment, are driving the pharmaceutical industry to implement quality assurance and process improvement techniques developed by the process systems engineering (PSE) community in the last three decades (Oksanen & Garcia-Munoz, 2010; Stephanopoulos & Reklaitis, 2011).

Among these techniques, the implementation of model predictive control (MPC) is undoubtedly one of the most effective ways to compensate the effect of disturbances onto the productivity of the process and the quality of the final product (Qin & Badgwell, 2003). An MPC algorithm performs an optimization calculation to provide the best *sequence of future moves* for the manipulated variables in order to keep the process at the desired state. This optimization calculation is based on a model that predicts the effect of a candidate sequence of moves in the manipulated variables; onto the metrics of interest (i.e. economic criteria, quality based or safety oriented).

Pharmaceutical applications of MPC are mostly found in areas where predictive models are available for the unit operations involved. A vast majority of the reported MPC applications have been in the crystallization field (Hermanto, Chiu, Woo, & Braatz, 2007; Liotta & Sabesan, 2004; Nagy, 2009; Pataki et al., 2012; Rohani, Horne, & Murthy, 2005); and only a few reported applications involving unit operations related to the manufacture of drug product like freeze drying (Pisano, Fissore, & Barresi, 2011).

The manufacturing of pharmaceutical drug product is still an area of opportunity for the application of MPC. Academics have already shown the potential of advanced control strategies in this sector (e.g. for roller compaction (Hsu, Reklaitis, & Venkatasubramanian, 2010)) and surely the field will continue evolving with industrial applications following soon (Troup & Georgakis, 2013).

In this work, we propose a feed-forward corollary approach to MPC for a *lot-driven-operation*; where there are no available manipulated variables in the process (due to regulatory constraints for example). These are special cases where the only variability available to be turned into a degree of freedom in a feed-forward controller is the lot-to-lot variability in the raw materials.

* Corresponding author. Current address: Eli Lilly and Company, Lilly Research Laboratories, Indianapolis, IN 46285, USA. Tel.: +1 (317) 651 5233.
E-mail address: sal.garcia@lilly.com (S. García Muñoz).

0098-1354/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.compchemeng.2013.09.020

Any *lot-driven-operation* starts with the allocation of raw materials for the next n lots of goods to be manufactured. Now, the manufacture of the product will require certain specific amounts of each raw material per lot produced. The inventory manager will decide on where to source the needed materials for each of the n lots to be produced (from the available lots of each ingredient in the current inventory). For a low volume product, n will typically be one or two; for a high volume product, n can be as high as the inventory and production process allows.

The method proposed in our work aims to provide guidance to this selection in order to minimize the variability in the quality of the end product. The main objective is to select the lots of materials to be blended according to their physical properties and cancel out undesired interactions across materials.

The idea of selecting materials based on the multivariate correlations in their physical and chemical properties was initially proposed by Muteki, MacGregor, and Ueda (2006, 2007); Muteki and MacGregor (2008) and has already been taken to practice for pharmaceutical applications to select the materials for the next *best lot* of product (Garcia-Munoz & Mercado, 2013).

Seeking to maximize the quality of the *next best lot* for the case of high volume product will result in the accelerated depletion of excellent quality raw-materials, potentially leaving only materials that are less desirable in inventory. The main problem is posed by the multivariate combination of physical properties across materials resulting in a poor quality end product, and does not owe to the individual materials being undesirable or out of specification. Although an elegant solution to this problem is the establishment of multivariate specifications (Duchesne & MacGregor, 2004); this becomes difficult (if not impossible) to implement when the interactions take place across materials from different vendors.

The methodology proposed in this paper extends the *next best lot* approach we proposed earlier (Garcia-Munoz & Mercado, 2013) to consider a horizon of n lots to be manufactured, hence the comparison with MPC. By considering this horizon of lots (rather than just the next one), our method allows the discretionary use of all materials to ensure that the quality of all the n lots is within specification.

This paper is organized as follows: In Section 2, we elaborate on the process description and the development of the mixture model used at the core of the optimization exercise. The objective function and the constraints are discussed in Section 3. The results from implementing this technique in a commercial setting are shared in Section 4, followed by our concluding remarks in Section 5.

2. Model development

The case study presented here involves the manufacture of an encapsulated drug product. After weighing and dispensing of the necessary ingredients, the material undergoes a granulation step followed by encapsulation. Due to limitations in equipment availability, the product can be held for some time between granulation and encapsulation; this time lapse is referred to as the *holding time*. All the process parameters that dictate the operation of this manufacturing train are fixed due to regulatory constraints. These constraints prevent us from using any process variable as part of a control strategy to compensate for disturbances. The only information available from a processing stand point is the environmental conditions of the cubicle where the operation took place (temperature and relative humidity). Needless to say, the formulation (i.e. composition) of the lot is also fixed.

From a materials perspective, the product requires four inactive ingredients plus the active pharmaceutical excipient (API – that accounts for 43.5% weight of the blend). Each material is characterized by a different number of properties, which were taken from

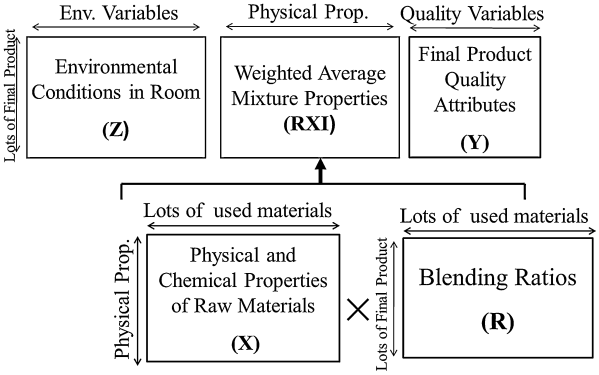

Fig. 1. Matrix representation of the data considered.

the certificate of analysis (CoA) of each lot. Finally, the final product is characterized by six quantities summarizing the results from the dissolution testing of the multiple capsules sampled from the lot (Table 1).

Data were gathered from 106 lots of drug product spanning 4 years of manufacturing experience. All this information is organized in a matrix form (Fig. 1). This system of matrices contains information (per ingredient) on which lots of raw material were used and in what quantity (*Blending Ratios* in matrix **R**); for each lot of final drug product. And for each lot of raw material used there was a record of its physical and chemical properties (**X**) as reported in the CoA. As proposed by Muteki et al. (2007) the blending ratios and the physical properties of the raw materials (matrices **R** and **X**) were combined using a weighted average into a single matrix (**RXI**). The environmental conditions are summarized in a matrix **Z** and the final quality of the product in matrix **Y**. It is also known at this point that the variability in the **Z** matrix is driven by seasonal effects (i.e. the **Z** matrix is predictable).

The strategy to take advantage of the lot-to-lot variability of the raw materials can only succeed if the variation in the physical properties of the raw materials is indeed influencing the final quality of the product. This was determined using a projection to latent structures (PLS) model to perform the regressions. A PLS model was chosen based on the interpretability of its parameters and the stability of these models upon inversion (Burnham, MacGregor, & Viveros, 1999;Tomba, Barolo, & Garcia, 2012).

In a PLS model the variables of the regressor and the response are both summarized by a smaller number of *latent variables* that are quantified in the *scores* of the model (**T**). The relationships across variables are represented by the loadings coefficients (**W***, **P** and **Q**). Scores and loadings are mathematically related to the original data as described in equation system 1 where $\mathbf{E_x}$ and $\mathbf{E_y}$ are the residuals.

$$\begin{aligned} [\mathbf{Z}\,\mathbf{RXI}] &= \mathbf{TP}^{\mathrm{T}} + \mathbf{E_x} \\ \mathbf{Y} &= \mathbf{TQ}^{\mathrm{T}} + \mathbf{E_y} \\ \mathbf{T} &= [\mathbf{Z}\,\mathbf{RXI}]\mathbf{W}^{*} \end{aligned} \tag{1}$$

In order to assess the correlations present in the data, three PLS models were built correlating the quality attributes of the product (**Y**) with the variability in (i) the environmental conditions (**Z**), (ii) the weighted average of the physical properties of the raw materials (**RXI**) and (iii) both.

For this particular case, the best prediction of the final quality of the product was obtained when both blocks of regressors (**Z** and **RXI**) were used (Table 2). This result led us to construct a strategy where the environmental conditions were used as a constraint in the optimization that guides the selection of the materials for a given campaign of n lots of final product.