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In-line monitoring of the primary drying phase of the freeze-drying process in vial by means of a Kalman filter based observer

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ABSTRACT

This paper is focused on the monitoring of the primary drying phase of the lyophilisation process of pharmaceuticals in vial. Monitoring is required to ensure that the maximum temperature of the product is maintained at a safe value in order to avoid denaturation, and the position of the moving front of sublimation has to be monitored since its evolution gives the state of progression of the primary drying. Furthermore, the information coming from the monitoring system, which includes the estimation of the transport coefficients, can be used in a control loop designed to minimise the drying time beside ensuring product quality.

To this purpose, a soft-sensor (observer) has been developed, based on the extended Kalman filter algorithm: it requires a model of the process (a simplified model is used in order to reduce the computational load) and some physical measurements (in this case the temperature of the product at the bottom of the vial, that can be measured by a thermocouple). The main issues arising in the design of this observer have been discussed. A detailed mono-dimensional model experimentally validated has been used at first to compare the results provided by the observer by means of numerical simulations, and then the results obtained in a pilot freeze-dryer are shown.

Keywords: Freeze-drying; Lyophilisation; Primary drying; Modelling; Monitoring; Extended Kalman filter

1. Introduction

Freeze-drying, or lyophilisation, is the process where water or another solvent is removed from a frozen product by sublimation. The lyophilisation technique consists of three main steps:

1. Freezing: the product to be dried is frozen at low temperature;
2. Primary drying: in this phase the ice is sublimated, generally operating under reduced pressure. Vapour originated at the moving sublimation front flows through the dried material into the lyophilisation chamber and a refrigerated trap connected to the chamber – the ice condenser – continuously removes it. In vial freeze-drying heat is continuously supplied to the product through an heating shelf; this is required in order to compensate for the energy required by the endothermic sublimation process.
3. Secondary drying: the last stage of the freeze-drying process is a desorption step where the residual moisture, which is strongly bounded by adsorption phenomena to the partially dried cake, is reduced to a low level ensuring long term product preservation at room temperature. This step is usually carried out at high vacuum and moderate temperature (+20 to +60 °C).

In most of the industrial freeze-dryers control actions are often based on empirical information obtained in previous

Abbreviations: DPE, dynamic parameters estimation; EKF, extended Kalman filter; MTM, manometric temperature measurement; PRT, pressure rise test; SDP, semi-definite positive.

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Nomenclature

$\mathbf{e}(t)$	error of estimation of the observer
$\mathbf{f}$	vectorial function giving the derivatives of the state
$\mathbf{h}$	vector of equations giving the state space equations of the measures
H	moving front position (m)
ΔH_s	enthalpy of sublimation (J kg^{-1})
k	thermal conductivity (J m^{-1} s^{-1} K^{-1})
k_1	effective diffusivity coefficient (m^2 s^{-1})
$\mathbf{K}(t)$	observer gain
K_v	overall heat transfer coefficient (J m^{-2} s^{-1} K^{-1})
L	total product thickness (m)
M	molecular weight (kmol kg^{-1})
p	pressure (Pa)
R	ideal gas constant (J kmol^{-1} K^{-1})
r	tuning parameter
$\mathbf{S}(t)$	matrix giving the solution of the dynamic Riccati equation
t	time (s)
T	Temperature (K)
T_B	frozen layer temperature at $z = L$ (K)
$\mathbf{u}$	vector of the control variables
$\mathbf{v}(t)$, $\mathbf{w}(t)$	white noises
$\mathbf{x}$	state space vector
$\mathbf{y}$	vector of the measured outputs of the system
z	axial coordinate (m)

Greek letters

α,β,γ,δ	variables defined by Eqs. (12)–(15)
Λ	matrix of tuning parameters for the Kalman observer
ϱ	mass density (kg m^{-3})

Subscripts

I	layer I, dried layer
II	layer II, frozen layer
c	chamber
e	effective
i	interface
meas	measured
shelf	heating shelf
w	water vapour

Superscripts

$\hat{}$	observer estimate
$\dot{}$	first time derivative

experimental runs carried out with the product of interest. Nevertheless, Guidance for Industry PAT (process analytical technology) issued by the US Food and Drug Administration in September 2004, encourage to develop in-line monitoring and control tools in order to improve the manufacturing process. The most important parameter to be monitored and to be controlled during primary drying is the temperature of the product. In fact primary drying should be carried out at a temperature below the eutectic point of the crystalline solute, to avoid formation of liquid. Many solutes, such as proteins, do not crystallise during freezing, remaining amorphous. The formation of a glass can be beneficial for the protein activity preservation; but, it makes the drying process more demanding in terms of process time and physical conditions, because the primary drying must be carried out below the glass transition temperature to avoid collapse of the cake structure. Another important variable that would be useful to monitor is the position of the sublimating interface, the evolution of which gives the state of progression of the primary drying. Mass transfer across the porous matrix of the product and heat transfer between the shelf and the vial are two other critical aspects that influence the drying time. Mass transfer is related to the temperature and pressure conditions and to the resistance of the dried cake to the vapour flow. Heat transfer is mainly linked to the composition and pressure of the gas phase in the lyophilisation chamber and to the geometry of the vial in the region of contact with the heating shelf.

The insertion of thin thermocouples in the vials is a widely used method to measure the product temperature. Moreover, if multiple thermocouples are inserted the position of the moving front can be monitored. In fact, as the sublimating interface passes in correspondence of the sensor, a change in the slope of the temperature profile is observed since the thermal conductivity of the frozen and dried layer is different. However, for practical reasons, only one thermocouple is generally used placed in close contact with the internal bottom of the vial, whose temperature is assumed representative of the whole product. The method proposed in this paper, based on the extended Kalman filter (EKF) concept, is able to determine the temperature of the product at any axial position, as well as the dynamic evolution of the sublimating interface, only exploiting the single point measure of the temperature at the bottom of the product. Some parameters related to mass and heat transfer are also estimated, that can be fed to an in-line predictive control system (Fissore et al., 2008). Furthermore, differently from manometric temperature measurement (MTM) like methods (for a review, see Velardi et al., 2008), this approach allows continuous monitoring either in one or several single vials placed in different positions, giving a direct in-line measure of the batch variance.

Most of the modern theories on the control of dynamic systems are actually based on a state space representation. This representation allows for the description of the system behaviour through the variation of its state. The state of a system can be defined as the minimum set of information needed to completely describe the system at a given time instant. The knowledge of the vector of the state is needed in order to apply the command law. This can be achieved by using physical sensors. However, in many cases due to cost consideration and physical constraints, the number and type of sensors could be very limited. An observer, or soft-sensor, combines a priori knowledge about the physical system – the model – with experimental data – the on-line measurements – to provide an on-line estimation of states and/or parameters.

The synthesis of observers for non-linear systems is generally a difficult task and many types of observers have been proposed in the literature. All the approaches proposed are based on the analysis of the observability (sensitivity of the output measurements with respect to state). The observability analysis yields to special forms of systems (called normal form, or canonical form). Among these canonical forms, linear systems up to output injection are systems whose dynamics can be splitted into two parts: a linear one with respect to state and a non-linear one which depends only on the output measurements (Krener and Isidori, 1983). For these systems, it is possible to design a Luenberger observer. Using a Kalman-like