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On the Design of a Fuzzy Logic—Based Control System for Freeze-Drying Processes

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ABSTRACT

This article is focused on the design of a fuzzy logic—based control system to optimize a drug freeze-drying process. The goal of the system is to keep product temperature as close as possible to the threshold value of the formulation being processed, without trespassing it, in such a way that product quality is not jeopardized and the sublimation flux is maximized. The method involves the measurement of product temperature and a set of rules that have been obtained through process simulation with the goal to obtain a unique set of rules for products with very different characteristics. Input variables are the difference between the temperature of the product and the threshold value, the difference between the temperature of the heating fluid and that of the product, and the rate of change of product temperature. The output variables are the variation of the temperature of the heating fluid and the pressure in the drying chamber. The effect of the starting value of the input variables and of the control interval has been investigated, thus resulting in the optimal configuration of the control system. Experimental investigation carried out in a pilot-scale freeze-dryer has been carried out to validate the proposed system.

Introduction

The number of pharmaceuticals and biopharmaceuticals requiring a freeze-drying stage in the manufacturing process is continuously increasing, mainly due to the higher stability of these molecules at solid state with respect to a liquid solution.[1,2]

When a product is freeze-dried, its temperature is first lowered in such a way that the liquid solvent (water, in most cases) is frozen (it has to be taken into account that only the "free water," i.e., the fraction of water not bound to product molecules, is frozen). Then, lowering the pressure, ice sublimation can occur (primary drying): in this stage, heat has to be supplied to the product as the sublimation of the ice is an endothermic process. Finally, the desired value of residual humidity in the product is obtained by further increasing the temperature of the product, thus causing the desorption of the fraction of water bound to product molecules (secondary drying).[3-6]

Because of the low operating temperatures, the freeze-drying process is expected not to impair product quality when processing thermolabile molecules such as drugs. Unfortunately, final product quality is preserved only if product temperature is maintained below a certain threshold value, that is, a characteristic of the product being processed, during the drying stages. In particular, the primary drying is the critical stage as the limit temperature is lower than in the secondary drying stage because of the higher content of water. The limit temperature is associated both to undesired chemical reactions and, in most cases, to the structural collapse of the dried cake, when amorphous products are processed.[7-12]

Besides, when freeze-drying a product, it has to be taken into account that the process can be time and energy consuming. As a consequence, the operating conditions of the process have to be carefully selected in such a way that drying time is minimized and the constraint on product temperature is fulfilled. (An additional constraint is about the sublimation flux, that has to remain below the value that causes choking flow in the duct connecting the drying chamber to the condenser, thus causing the loss of pressure control in the chamber,[13-15] but in a properly designed equipment, this constraint is generally respected).

In a freeze-dryer, there are 2 variables that can be manipulated, namely the pressure (P_c) in the drying chamber, where the product is loaded, and the temperature (T_{fluid}) of the fluid that flows in the shelves above which the containers of the product are loaded, and that is used to lower product temperature in the freezing stage and to heat the product in the drying stages. It is necessary to select the

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List of Symbols

A_{K_v}	parameter used to calculate K_v, W m^{-2} K^{-1}
A_{R_p}	parameter used to calculate R_p, m s^{-1}
a, b, c	parameters of the membership function
B_{K_v}	parameter used to calculate K_v, W m^{-2} K^{-1} Pa^{-1}
B_{R_p}	parameter used to calculate R_p, s^{-1}
C_{K_v}	parameter used to calculate K_v, Pa^{-1}
f	membership function
ΔH_s	heat of sublimation, J kg^{-1}
J_q	heat flux to the product, W m^{-2}
J_w	sublimation flux, kg m^{-2} s^{-1}
K_v	heat transfer coefficient, W m^{-2} K^{-1}
k_{frozen}	thermal conductivity of the frozen product, W m^{-1} K^{-1}
L_{dried}	thickness of the dried product, m
L_{frozen}	thickness of the frozen product, m
P_{Baratron}	chamber pressure measured by a capacitance gauge, Pa
P_c	chamber pressure, Pa
P_{Pirani}	chamber pressure measured by a thermoconductive gauge, Pa
$p_{w,c}$	water partial pressure in the drying chamber, Pa
$p_{w,i}$	water partial pressure at the interface of sublimation, Pa
Q_R	rate of product temperature change, K s^{-1}
R_p	resistance of the dried product to vapor flux, m s^{-1}
$R_{p,0}$	parameter used to calculate R_p, m^{-1}
T	product temperature, K
T_B	temperature of the product at the bottom of the vial, K
T_{fluid}	temperature of the heating fluid, K
T_i	temperature of the product at the interface of sublimation, K
T_{lim}	threshold value for product temperature, K
t	time, s
x	input variable of the membership function
y	output variable of the membership function
Greeks	
ρ_{dried}	effective density of the dried product, kg m^{-3}
ρ_{frozen}	effective density of the frozen product, kg m^{-3}

optimal values of T_{fluid} and P_c not only when designing the process for a new product but also during manufacturing, to account for process disturbances.

Basically, there are 2 approaches to design a freeze-drying process. It is possible to optimize the process off-line, using a mathematical model of the process to calculate the design space,[16-24] or to optimize the process in-line, in a single run, using a control system.[25-28] During manufacturing, the use of a control system allows modifying easily the operating conditions to face process disturbances, whereas in case the system is optimized off-line, suitable safety margins are required in such a way the process is sufficiently “robust” to preserve product quality also in case of disturbances. The advantages and disadvantages of both approaches have been extensively discussed by Pisano et al.[29] Essentially, the main problem related to the off-line optimization is that a (sometimes) time-consuming experimental investigation is required to estimate model parameters, and in case the cycle has to be sufficiently robust towards process disturbances, then the operating conditions that are identified can be very far from the optimal ones. On the other side, when using a control system, it is necessary to use a suitable monitoring system to estimate in-line accurately the values of model parameters, and this can be a really challenging task. Both the measurement of product temperature with the soft-sensor algorithm[30-37] and the pressure rise test[38-44] have been used to this purpose.

This article aims to describe a new system based on fuzzy logic to optimize in-line a freeze-drying process, both in the stage of process design and during manufacturing. The control of fluidized-bed[45] and high shear[46] granulation processes, the modeling of skin permeability,[47] the optimization of tableting processes,[48] and the evaluation of cake quality of freeze-dried products[49] are examples of application of fuzzy logic in the pharmaceutical field. As it will be shown in the following, the use of a fuzzy logic–based controller in a freeze-drying process allows obtaining the optimal values of the process-manipulated variables (T_{fluid} and P_c) in just one run, without using any expensive measuring device (a part from a thermocouple, i.e., generally available in any freeze-dryer, at least in those laboratory- and pilot-scale units used for process development). Moreover, no mathematical models are involved in the calculation of the control actions, and thus, the problem of the in-line estimation of model parameters is avoided. Finally, the control laws presented as the main result of this study can be readily and safely used for most of the products currently freeze-dried (it is only required to know the limit temperature). Thus, the system that will be described, and whose performance will be presented and discussed in the following sections, stands out as a simple and effective tool for process control and optimization, that allows coping with the disadvantages of the methods based on model-based off-line and in-line optimization. Mathematical modeling will be used at first for the development of the control laws and for the off-line validation. Then, experiments carried out with various products will be presented, aiming to validate the proposed method.

Materials and Methods

Fuzzy Logic Fundamentals and Application to Freeze-Drying

A control system for a given process can be regarded as a set of IF-THEN rules, combined using the AND or OR operators, and relating the monitored (input) and the manipulated (output) variables. Such inference system can be based on a simple true or false Boolean logic. As an example, considering the freeze-drying process, a typical rule can be the following: IF product temperature is lower than the threshold value, THEN the temperature of the heating fluid can be increased (of a certain amount). Process knowledge is obviously required when formulating the various rules, for example, in this case, it is required to know that when the temperature of the heating fluid is increased, then the temperature of the product increases. As proposed by Zadeh,[50] the fuzzy logic allows doing something more complex, that is thus expected to give better results as the inference system is based now on the degree of membership of the input–output variables to a certain statement. For the previous example, this means that not only the fact that product temperature is higher than the threshold value but also the amount of the excess temperature is considered when calculating the temperature of the heating fluid.

For the freeze-drying process under investigation, 2 fuzzy logic–based inference systems were designed and run simultaneously. The first is based on the manipulation of the heating fluid temperature as a function of the difference between product temperature (T) and the threshold value (T_{lim}) and on the rate of product