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Constructing regions of attainable sizes and achieving target size distribution in a batch cooling sonocrystallization process

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ABSTRACT

The application of ultrasound to a crystallization process has several interesting benefits. The temperature of the crystallizer increases during ultrasonication and this makes it difficult for the temperature controller of the crystallizer to track a set temperature trajectory precisely. It is thus necessary to model this temperature rise and the temperature-trajectory tracking ability of the crystallizer controller to perform model-based dynamic optimization for a given cooling sonocrystallization set-up. In our previous study, we reported a mathematical model based on population balance framework for a batch cooling sonocrystallization of L-asparagine monohydrate (LAM). Here we extend the previous model by including energy balance equations and a Generic Model Control algorithm to simulate the temperature controller of the crystallizer that tracks a cooling profile during crystallization. The improved model yields very good closed-loop prediction and is conveniently used for studies related to particle engineering by optimization. First, the model is used to determine the regions of attainable particle sizes for LAM batch cooling sonocrystallization process by solving appropriate dynamic optimization problems. Then the model is used to determine optimal operating conditions for achieving a target crystal size distribution. The experimental evidence clearly demonstrates the efficiency of the particle engineering approach by optimization.

1. Introduction

Producing crystals consistently with desired attributes such as size, purity, polymorphic form, etc., is a challenging task in a crystallization process. Controlling these attributes is essential both for product effectiveness as well as efficient downstream processing. Achieving desired product attributes in a crystallization process is considered to be difficult due to the stochastic nature of the nucleation event and the limited number of manipulated variables available to exercise control over the process. In this context, the use of ultrasound (US) appears to be an important additional manipulated variable to control a crystallization process [1,2]. The application of US to crystallization processes has been shown to have several interesting benefits such as faster and uniform primary nucleation [3–5], reduction of agglomeration [6], control of polymorph [7–9], production of narrow and uniform crystal size distribution (CSD) [10–14], superior crystal habit [15], etc. US can also be used for generation of internal seed and thus bypassing the use of conventional seeding [14].

A desired CSD can be obtained by following suitable operating policies (cooling rate, antisolvent addition rate, sonication time, etc.) for a given crystallization process. Various approaches have been proposed for designing such appropriate operating policies which are mainly classified into two categories: the model-based approach and the model-free approach [16]. The model-based design approach involves the use of a mathematical model describing the crystallization dynamics along with appropriate optimization techniques to determine optimal control trajectories such as temperature versus time or antisolvent addition rate versus time. This category also includes approaches that consider uncertainties in model structure to provide robust optimal operating policies [17,18]. The model-free (or direct) design approach uses supersaturation control [19,20], concentration feedback control [21], or direct nucleation control [22] to operate the crystallization process within the metastable zone. Model-based optimization has been extensively studied and has emerged as a powerful tool to determine the optimal recipe to achieve product with desired attributes [23–31]. Generally, properties related to desired crystal size distribution have been considered as common objective functions. Recently, objective functions related to crystal shape has also been considered in order to achieve desired crystal shape [32–34]. Although there are now some reports on population balance modelling of sonocrystallization process [6,35–38], the model-based optimization of sonocrystallization process still remains unexplored.

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Nomenclature

A	total heat transfer surface area, m^2
B	birth rate
b	breakage distribution function
b_I	nucleation order
C	dissolved solute concentration, g/g
C^*	equilibrium concentration, mol/m^3, g/g
C_c	molar density, mol/m^3
C_o	initial concentration, g/g
C_p	heat capacity of the solution, kJ/(kg K)
C_{pj}	heat capacity of water, kJ/(kg K)
D	death rate
ΔH_c	heat of crystallization, kJ/kg
F_j	cooling water flow rate, m^3/min
G	growth rate, μm/min
g	growth order
J	nucleation rate, 1/(m^3 min)
k_{bI}	nucleation rate coefficient
k_g	growth rate coefficient
k_{J1},k_{J2}	empirical parameters
k_v	volume shape factor
L	crystal size, μm
M	mass of the solution, kg
n	number density, 1/(m^3 μm)
p_{break}	breakage kernel
P_{US}	ultrasonic power, kJ/min
S	supersaturation ratio
T	temperature, ˚C
t	time, min
U	overall heat transfer coefficient, kJ/(m^2 min K)
V_j	jacket volume, m^3

Greek letters

γ	breakage frequency
γ_o	selection coefficient
μ_i	ith moment of CSD
ρ_c	crystal density, g/m^3
ρ_j	water density, g/m^3

Superscript and subscript

break	breakage
ind	induced
max	maximum value
min	minimum value
prim	primary
prop	property

Abbreviations

CSD	crystal size distribution
GMC	Generic Model Control
ID	internal diameter
LAM	L-asparagine monohydrate
US	ultrasound

This work focusses on various aspects of model-based optimization studies related to particle engineering of a batch cooling sonocrystallization process. As a model system, we consider the batch cooling sonocrystallization of L-asparagine monohydrate (LAM), a non-essential amino acid that plays an important role for human metabolism. Recently, we reported a population balance model for ultrasound-assisted batch cooling crystallization of LAM [38] and in this work, we use the experimentally validated model to perform computational and experimental studies related to particle engineering of the process by model-based optimization. The temperature of the crystallizer increases during ultrasonication and this makes it difficult for the temperature controller of the crystallizer to track a set temperature profile precisely. It is thus necessary to consider the closed-loop simulation of the crystallizer in order to model this temperature rise and controller's temperature tracking ability during application of US for finding optimal operating recipes. We, therefore, augment our previous population balance model by including energy balance equations for the crystallizer and cooling jacket into the population balance model and then modelling the temperature control system of the crystallizer by a Generic Model Control (GMC) algorithm. The improved model is then used to determine the optimal cooling profiles and sonication time for the crystallization process using various objective functions that represents product characteristics. Specifically, we first use the model to determine the regions of attainable particle sizes for batch cooling sonocrystallization process by solving appropriate dynamic optimization problems. Then we use the model to determine optimal operating

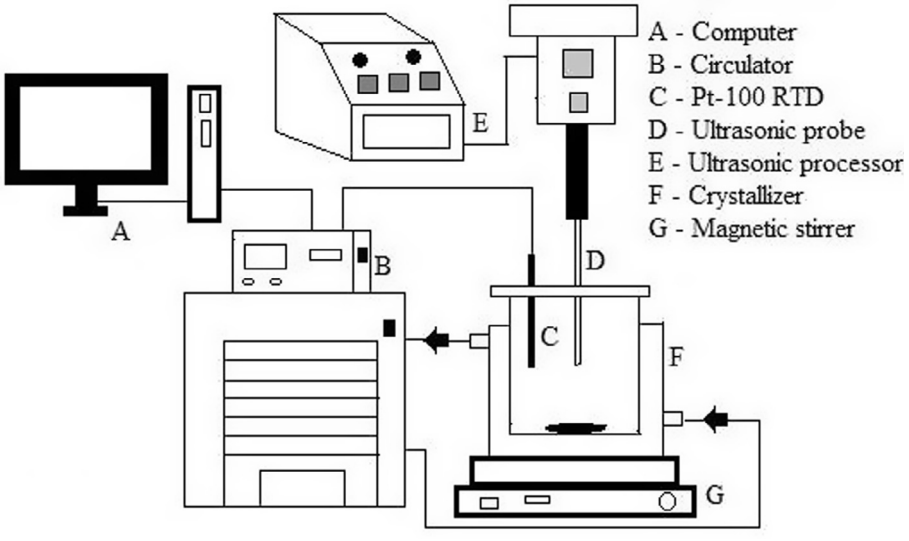

Fig. 1. Experimental set-up.