Contents lists available at ScienceDirect

Chemical Engineering Research and Design

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

Integrating crystallization with experimental model parameter determination and modeling into conceptual process design for the purification of complex feed mixtures

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ARTICLE INFO

Article history:
Received 23 August 2017
Received in revised form 30 January 2018
Accepted 17 March 2018
Available online 26 March 2018

Keywords:
Crystallisation
Purification
Modelling
Fermentation broth

ABSTRACT

In this study, crystallization process simulation combined with experimental model parameter determination at lab-scale is investigated in order to allow the integration of crystallization unit operation into conceptual process design for the purification of complex mixtures and possibly assist in formulation.

A one-dimensional population balance model is combined with experiments, which are selected and carried out as a typical example for an industrial fermentation broth (e.g. vanillin), focusing on determination of solubility and growth kinetics as well as kinetics of agglomeration and breakage. Model parameter determination and model validation show that the named effects are adequately described by the model. Hence, model-based process design of purification by crystallization and particle formation enabling integration into formulation considering relevant effects regarding a complex feed mixture becomes possible within a conceptual process design. Further applications are under consideration.

1. Introduction

Modeling of crystallization for purification and particle design has been practiced for more than 30 years and therefore, different models exist focusing on various aspects of crystallization processes. Along with process models, there are thermodynamic models for solubility prediction (Abraham et al., 2010; Brozio et al., 2008; Eckert and Klamt, 2002; Lange et al., 2016; Wollenhaupt and Baumann, 2014) as well as models for crystal shape prediction (Briesen, 2006; Tilbury et al., 2016). Many process models consider one or two of the aspects of crystallization such as growth kinetics (Abbas and Romagnoli, 2007; Codan et al., 2013; Miller and Rawlings, 1994), nucleation kinetics (Jiang and ter Horst, 2010; Maggioni and Mazzotti, 2015; Schwarzer et al., 2006), agglomeration (Hounslow et al., 2013; Lindenberg et al., 2008; Ochsenbein et al., 2015), breakage (Das, 2016; Gahn and Mersmann, 1999) and impurity adsorption (Borsos et al., 2016; Févotte and Févotte, 2010). Fewer models also combine several of these aspects (Balakin et al., 2010; Bertin et al., 2016; Besenhard et al., 2014). The mathematical solution of population balance models is likewise well-known (Ramkrishna, 2000; Randolph and Larson, 1971).

Experimental design of crystallization processes starts with crystal form and morphology selection based on formulation and galenic product requirements as well as crystal size and size distribution, followed by solubility measurement and kinetics optimization (Wieckhusen, 2013). Solid form selection focuses on decision for the desired polymorph and if required on the choice between salt, hydrate or solvate. Solubility is determined by either isothermal or polythermal methods (Lorenz, 2013), exhibiting different advantages and drawbacks. With solubility, the mass balance of the crystallization process can easily be calculated. Kinetics optimization comprises design of seeding strategy (Beckmann, 2000; Kubota et al., 2001) and supersaturation profile (Fiordalis and Georgakis, 2010; King et al., 2015; Mohameed et al., 2002).

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https://doi.org/10.1016/j.cherd.2018.03.029

Nomenclature

Symbols

A	Area of thermal jacket (m^2)
A_{Agg}	Agglomeration parameter (–)
A_{Br}	Breakage parameter (–)
A_{eq}	Solubility parameter (g/g)
B	Birth term in population balance (1/(μm s))
B_{Agg}	Birth distribution agglomeration (–)
B_{Br}	Birth distribution breakage (–)
B_{eq}	Solubility parameter (g/g)
c	Concentration of target component in liquid phase (g/g)
c_{eq}	Solubility (g/g)
c_p	Specific heat capacity (at constant pressure) (J/(kg K))
c_{Part}	Particle concentration (g/l)
$c_{Part,ref}$	Reference particle concentration (g/l)
$c_{S,i}$	Concentration of side component i in liquid phase (g/g)
D	Death term in population balance (1/(μm s))
$D_{i,j}$	Diffusion coefficient (m^2/s)
D_{Agg}	Death distribution agglomeration (–)
D_{Br}	Death distribution breakage (–)
e_{Agg}	Agglomeration exponent parameter (–)
e_{Br}	Breakage exponent parameter (–)
d_{St}	Diameter of stirrer (m)
g	Growth kinetics exponent (–)
G	Growth rate (μm/s)
k_A	Surface shape factor (–)
k_G	Growth kinetics parameter (μm/s)
k_V	Volumetric shape factor (–)
k_W	Heat transfer coefficient (W/(m^2 K))
m_C	Mass of crystals (kg)
m_{CT}	Mass of target component in crystals (kg)
m_I	Mass of seed crystals (kg)
m_S	Mass of suspension (kg)
n	Stirrer rate (1/s)
N_i	Number of particles in class i (–)
N_{Cl}	Number of particle size classes (–)
N_{tot}	Total number of particles (–)
Ne	Newton-number (–)
p	Relative particle number (number fraction) (–)
pu	Purity (–)
q_0	Number-based particle size density distribution (1/μm)
Q_0	Number-based particle size sum distribution (–)
q_3	Volume-based particle size density distribution (1/μm)
Q_3	Volume-based particle size sum distribution (–)
q_{Br}	Breakage distribution matrix (1/μm)
$\dot{Q}_{Cryst}$	Enthalpy of crystallization (W)
$\dot{Q}_{St}$	Energy input by stirrer (W)
$\dot{Q}_{Cool}$	Heat removed by cooling (W)
r_{Br}	Breakage rate (1/s)
S	Supersaturation (–)
t	Time (s)
t	t value of student distribution (–)
T	Temperature (°C)
T_C	Temperature of cooling agent (°C)
ΔT_r	Random temperature deviation (°C)
V_S	Volume of suspension (m^3)
x	Particle size (μm)
$x_{50,0}$	Median value of a particle size distribution q_0 (μm)
$x_{50,3}$	Median value of a particle size distribution q_3 (μm)
Δx	Class width (μm)
Δx_{50}	Relative deviation of median value of a particle size distribution (μm)
y	Particle size of second particle in agglomeration (μm)

Greek symbols

β	Collision kernel (–)
$\dot{\gamma}$	Shear rate (1/s)
Δ	(Measurement) deviation (–)
ν	Kinematic viscosity (m^2/s)
ρ	Density (kg/m^3)

Subscripts

0	Initial
Agg	Agglomeration
Br	Breakage
Cal	Calibration
D	Dilution
eq	Equilibrium
i	Component
r	Random
ref	Reference
T	Temperature
tot	Total

If completely experimental, this design is based on heuristics and equations for calculation of seed mass, cooling profile and evaporation rate (Mersmann and Kind, 1985; Warstat and Ulrich, 2007).

In order to enable experimental crystallization process development, various measurement methods are developed and respective devices are evaluated in the literature. These methods and devices focus on liquid phase concentration measurement (Lindenberg et al., 2012; Yang and Rasmuson, 2012) as well as on particle size distribution measurement (Borchert et al., 2014; El Arnaout et al., 2016; Schorsch et al., 2014). Another field within experimental process development is on determination and evaluation of nucleation kinetics (Kubota, 2008; Mitchell et al., 2011a; Yang et al., 2014; Yang and Florence, 2017).

Along with the development of crystallization design methods, appropriate equipment is built and characterized. Besides the classical stirred tank, new trends like flash-crystallization (Gebauer et al., 2016), continuous crystallization in a coiled flow inverter (Hohmann et al., 2016) and gassing crystallization (Kleetz et al., 2016) are under research. Currently, there is a focus on continuously operated apparatuses (Besenhard et al., 2015; Klutz et al., 2015; Power et al., 2015). For characterization and comparison of the newly developed apparatuses, relatively simple systems like inorganic salts or small organic molecules are chosen. Nevertheless, purification by crystallization is another field of research (Ahmad and Ulrich, 2016; Münzberg et al., 2016; Weber et al., 2015; Zu et al., 2016).

In contrast, the aim of this study is to enable especially process integration of crystallization for purification out of complex feed mixtures. The focus is laid on pharmaceutical or nutrition crystal products, which are in a regulated environment. Hence, there exist requirements regarding particle size distribution as well as particle purity. These properties should be predicted with an accuracy that allows to meet the regulatory requirements, and the design of pretreatment steps like liquid–liquid extraction or chromatography. Each product or product type has a specific range of particle size, which is usually several 100 μm in width (Fonteyne et al., 2014; Rohrs et al., 2006; Sun and Grant, 2004)