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Semibatch reaction crystallization of salicylic acid

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A B S T R A C T

Reaction crystallization of salicylic acid has been investigated by experiments and modeling. In the experimental work, dilute hydrochloric acid has been added to an agitated aqueous solution of sodium salicylate in 1 L scale, and product crystals have been characterized by image analysis. The results show that the product crystal number mean size at first increases with increasing agitation rate but then gradually decreases again at further increase in stirring rate. At lower stirring rate, larger crystals are obtained when the feeding point is located close to the agitator instead of being located out in the bulk solution. The mean crystal size increases with decreasing feeding rate and with decreasing reactant concentrations. There is a decrease in mean size with increasing feed pipe diameter. These trends in the experimental results show great similarity with previous results on benzoic acid. The experimental results have been examined by a population balance model accounting for meso and micro mixing, and crystal nucleation and growth rate dispersion. It is found that the crystallization kinetic parameter estimation is quite complex, and the objective function hyper surface contains many different minima. Hence, parameter estimation has to rely on a combination of mathematical optimization strategies and a scientific understanding of the physical meaning of the parameters and their relation to current theories. As opposed to our previous work on benzoic acid, it has not been possible to find a set of kinetic parameters that provides for a good description of all experimental data.

Keywords: Crystallization; Hydrodynamics; Mixing; Pharmaceuticals; Population balance; Salicylic acid

1. Introduction

Reaction crystallization or precipitation is used in the production of both inorganic and organic compounds, for example organic fine chemicals and photographic materials. A common procedure is to feed one reactant into an agitated solution of the other reactant in a semi-batch (or fed-batch) process. In reaction crystallization processes, the solubility of the formed compound is normally low or very low, and a region with high supersaturation and subsequent rapid nucleation and growth will form around the feed point. Nucleation starts before the solution has been completely homogenized, and the crystallization proceeds in a partially segregated solution. The mixing conditions in the crystallizer will have a significant influence on the final product characteristics.

A broader review of the area has been given by Ståhl and Rasmuson (2009). The semi-batch reaction crystallization of benzoic acid have been investigated in several experimental studies of our research group (Åslund and Rasmuson, 1992; Torbacke and Rasmuson, 2001, 2004), and the kinetics of crystallization and aging of benzoic acid have also been studied, based on experiments and population balance modeling (Ståhl et al., 2001, 2004). In the semi-batch experiments in 1 L scale (Åslund and Rasmuson, 1992), the product weight mean size clearly decreases at increasing reactant concentrations and increasing feeding rate. The intensity of mixing is found to have a significant influence on the product weight mean size. At low agitation the product weight mean size increases with increasing agitation rate, however reaches a maximum and then decreases again with further increase in the agitation.

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Notations

B	nucleation rate, #/m^3 s
c	solute concentration, mol/m^3
c^*	solubility, mol/m^3
CV_g	coefficient of variation for the growth rate activity distribution
d	feed pipe diameter, m
$D(S)$	driving force function
E	engulfment rate constant, 1/s
F	objective function
G	crystal growth rate = dL/dt, m/s
g	exponent in growth rate expressions
K_{p1}	primary nucleation rate parameter, #/m^3 s
K_{p2}	primary nucleation rate parameter
k_g	growth rate constant, m/s
$\bar{k}_g$	average growth rate constant, m/s
k_v	volume shape factor
L	characteristic crystal size, m
$\bar{L}_N$	number mean size, m
n	population density, #/m m^3
$\tilde{n}_i$	total population density of subpopulation i, #/m
P_g	growth rate activity distribution
R	residual
S	supersaturation ratio, c/c*
T	temperature, K
t	time, s
t_{micro}, t_{meso}	micro- and mesomixing time constants, s
V	volume, m^3

Greek letters

ε	energy dissipation rate, W/kg
ν	kinematic viscosity, m^2/s
ρ	crystal density, kg/m^3
σ_g	growth rate activity standard deviation
σ_L	standard deviation of size distribution

Larger crystals are obtained if the feed point is in the intensively mixed outflow region of the agitator, instead of in the bulk of the tank or at the surface. In the work of Torbacke and Rasmuson (2004) in 10 L scale we also investigated the influence of the feed pipe diameter. At longer feeding times, the product weight mean size decreased with increasing feed pipe diameter. At shorter feeding times, the influence was more complex. Overall, the experimental results show that also mesomixing has a decisive influence on the experimental results, in that the product weight mean size depends on the total feeding time and the feed pipe diameter.

In the work of Ståhl and Rasmuson (2009), a population balance model is developed over single-feed semi-batch reaction crystallization of benzoic acid. The model accounts for chemical reaction, micro- and mesomixing, primary nucleation, crystal growth and growth rate dispersion. When the mixing is described by the engulfment model and growth rate dispersion is accounted for, the model quite well captures the influence on the product weight mean size of reactant concentrations, agitation rate, feed point location, feed pipe diameter, total feeding time and crystallizer volume. The kinetics of nucleation and crystal growth are evaluated from experimental data by non-linear optimization.

In the present study, new experimental results over semi-batch reaction crystallization of salicylic acid are presented,

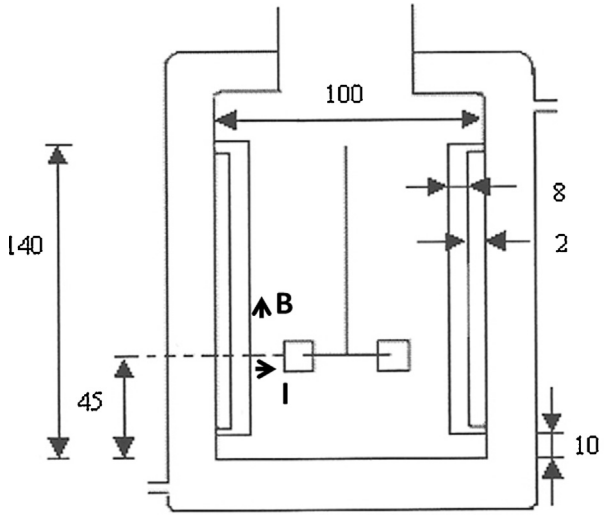

Fig. 1 – Geometry and dimensions (mm) of the stirred semi-batch reaction crystallizer, and feed point locations (B) and (I).

and the previous model of Ståhl and Rasmuson (2009) is evaluated. For this case, it turns out that the model is less capable of representing the influence of agitation, and in addition the fitting of the model to the data is more complex. This is analyzed and discussed in the paper.

2. Experimental work

Dilute hydrochloric acid is fed to an agitated, aqueous solution of sodium salicylate, in a semi-batch reaction crystallization process.

2.1. *Apparatus*

A flat-bottomed and jacketed 1 L glass tank reactor equipped with four baffles of stainless steel and of dimensions given in Fig. 1 was used during the experiments. A six-blade disk Rushton turbine of stainless steel is used at rotational speeds from 100 to 1600 rpm. The impeller along with its dimensions is shown in Fig. 2. The feeding point can be either inside the liquid bulk (B) or at the exit stream of the impeller (I), and both are marked in Fig. 1 by an arrow showing the feeding direction, and the feeding point at the tip of the arrow. Feeding into the bulk is done with the pipe outlet kept 20 mm from the wall, halfway between the two baffles and 20 mm above the impeller blade, while feeding at the impeller is done by keeping the pipe outlet approximately 2 mm below the turbine blade and 5 mm from the blade tip in the horizontal direction. The feed pipes used were acid resistant metals with inner diameters of 1.0 mm, 2.8 mm and 3.8 mm respectively. Feeding is done by a two-piston pump (Desaga 2000).

2.2. *Procedures*

The experiments are carried out at 30 °C. The sodium salicylate solution and the distilled water used to dilute the hydrochloric acid are filtered through a 0.22 μm membrane filter before the experiment. In all experiments, the sodium salicylate solution is saturated with salicylic acid. The hydrochloric acid is fed into the agitated sodium salicylate solution in stoichiometric amount, i.e. number of moles of hydrochloric acid at the end of each experiment is equal to