**Modeling solid-state deracemization via temperature cycles**

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**Highlights**

* Mathematical model of solid-state deracemization via temperature cycles was developed.
* The effect of the model parameters was investigated.
* Favorable conditions were identified as a function of the model parameters.

**1. Introduction**

Although preferential crystallization is a standard industrial process to obtain enantiopure crystals of conglomerate forming compounds, its maximum theoretical yield is 50%, unless one adds to it recycle and racemization steps [1]. On the contrary, one can produce an enantiopure powder from an initially racemic one through solid-state deracemization by exploiting several techniques [1,2]. Among such techniques, that based on temperature cycles is a promising candidate for industrial applications due to the simplicity of the setup required [1, 3, 4]. Because of the complexity of the process, its optimal implementation requires an accurate and reliable mathematical model [3].

Extending our isothermal population balance based model of attrition-enhanced deracemisation [3], we have developed a non-isothermal model to provide a clear explanation of the phenomena involved in the process [5]. Moreover, this model aims at explaining the sensitivity to variations in the model parameters, such as the breakage rate, the agglomeration rate, etc. that is challenging to be experimentally investigated.

**2. Methods**

We describe the evolution of the crystals during temperature cycles using a population balance model. The model describes the interplay of several phenomena (size-dependent solubility, crystal growth and dissolution, agglomeration, attrition and racemization) accounting for the dependence of their thermodynamic and kinetic parameters on the crystal size and on the temperature.

**3. Results and discussion**

We have developed a non-isothermal model, assuming to operate with an ideal temperature controller, hence the specified time-dependent temperature profile can be used instead of modeling heat transfer and temperature evolution through an energy balance. By identifying the relevant variables and their corresponding characteristic values, we have also derived the non-dimensional equations associated to the non-isothermal model. The nondimensional model allows to study the deracemization process in a quasi-universal manner, without the knowledge of the physical and chemical parameters, which are dependent on the specific system considered.

Using the PBE-model that we have introduced, we have simulated temperature cycles in batch crystallizers. The model is characterized by several physicochemical parameters, additionally, the outcome of the process depends on the initial and on the operating conditions. The effect of the process parameters was shown to compare well qualitatively with the experimental results that were investigated in a systematic way previously by our group [1]. The focus of this contribution is to investigate the effect of the model parameters on the process, e.g. the rate of breakage, the parameters of the agglomeration kernel, the rate of racemization, etc.



**Figure 1.** Evolution of the enantiomeric excess along the nondimensional time during deracemisation via temperature cycles. The magenta line indicates the generally utilized temperature profile (the line is not in scale with the values of the enantiomeric excess).

Various research groups studied experimentally how varying the operating temperature range or changing the cooling rate influence the process for different model compounds [1,4]. A thorough system parameter analysis can provide information on how to apply the role of initial asymmetry for different compounds to obtain the pure enantiomer. This analysis requires numerous simulations varying the model parameters that are associated with the chemicophysical properties of various model systems and their relative values that can vary for each substance. Therefore, we performed simulations to analyze the response of the system in a wide range of model parameters. With the help of the model these effects were evaluated and quantified based on the productivity.

**4. Conclusions**

We investigated the influence of several model parameters on deracemization via temperature cycles. Using the model the feasible and the optimal design spaces were identified.

**References**

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