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Mandelic Acid Single-Crystal Growth: Experiments vs Numerical Simulations

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Abstract. Mandelic acid is an enantiomer of interest in many areas, in particular for the pharmaceutical industry. One of the approaches to produce enantiopure mandelic acid is through crystallization from an aqueous solution. We propose in this study a numerical tool based on lattice Boltzmann simulations to model crystallization dynamics of (S)-mandelic acid. The solver is first validated against experimental data. It is then used to perform parametric studies concerning the effects of important parameters such as supersaturation and seed size on the growth rate. It is finally extended to investigate the impact of forced convection on the crystal habits. Based on there parametric studies, a modification of the reactor geometry is proposed that should reduce the observed deviations from symmetrical growth with a five-fold habit.

AMS subject classifications: 76T20

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1 Introduction

Mandelic acid is an aromatic alpha-hydroxy acid, with formula $C_8H_8O_3$. It is a white crystalline powder that is soluble in water and most common organic solvents. It has a density of 1.3 g/cm^3 and molecular weight of 152.5 g/mol. It is particularly important in the pharmaceutical industry for the organic synthesis of pharmaceutical components. For instance an ester of mandelic acid is essential to produce homatropine, used in eye drops as both a cycloplegic and mydriatic substance. In addition, it is also popular in the

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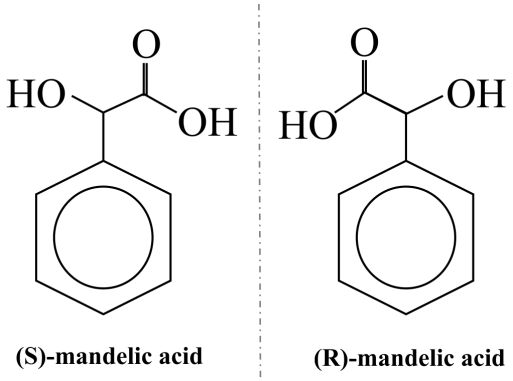

Figure 1: Molecular structure of mandelic acid enantiomers.

production of face peeling components [49], urinary tract infection treatments [5], and for oral antibiotics [44]. In toxicological studies, the concentration of styrene or styrene oxide is quantified by converting it into mandelic acid.

Mandelic acid exists in two enantiomeric forms as shown in Fig. 1, (S)- and (R)- mandelic acid. Most practical applications require the enantiopure form [5]. Amongst the different approaches to separate enantiomers, crystallization process such as classical resolution and preferential crystallization approaches are frequently used [30]. In such separation processes, the properties of the crystalline products such as crystal size and shape are largely determined by the growth process, which in turn depends on the crystallization conditions. In the pharmaceutical industry, the resulting crystal morphology is often of great importance, since it influences the rate of dissolution and the absorption of drugs. Compressibility, hardness, and flow properties of the drug are also strongly dependent on the crystal form [16]. Accurate investigations regarding crystal growth are difficult because the growth process varies greatly even under similar conditions: *crystal growth dispersion* is the term used to describe the fact that crystals, although initially of same shape and size, can rapidly grow differently even under the same growth conditions [31,45]. The main reason for these growth differences is probably related to minute tensions and deformations, leading in turn to minimal structural differences [17]. Other reasons are accidental deposits, or deposits of foreign bodies on the growing crystals' surface, which lead to incorporation into the crystal and ultimately different growth. A proper understanding of growth conditions and their effect on the final product is therefore essential to design and scale-up production units for enantiopure substances.

A lot of experimental studies have been conducted concerning crystallization-based enantioseparation process including growth kinetics of mandelic acid, e.g. [1, 10–13, 30, 36, 45]. However, numerical studies regarding crystal habit and size of enantiopure S-mandelic acid remain scarce. The phase-field method has been shown in general to be a powerful tool for modeling structural evolution of materials and crystals. It is now widely used for modeling solidification [4,35] and grain growth [8,26,47,50]. The phase-field approach has also been used in the context of the lattice Boltzmann method, now