**Kinetics of Crystallization in Solid Solution Forming Systems**

Maksymilian Olbrycht1\*, Maciej Balawejder2, Heike Lorenz3, Andreas Seidel-Morgenstern3,4, Wojciech Piątkowski1, Dorota Antos1

*1- Department of Chemical and Process Engineering, Rzeszow University of Technology, 35-959 Rzeszow/PL; 2- Chair of Chemistry and Food Toxicology, University of Rzeszow, 35-601 Rzeszow/PL; 3- Max Planck Institute for Dynamics of Complex Technical Systems, 39106 Magdeburg/DE; 4-Faculty of Process and Systems Engineering, Otto von Guericke University Magdeburg, 39106 Magdeburg/DE*

*\*m.olbrycht@prz.edu.pl*

**Highlights**

* Separation of stereoisomers by crystallization.
* SLE for two selected solid solution forming systems.
* Crystallization kinetics for the two systems.

**1. Introduction**

A significant number of the drugs currently in use contain chiral substances as active pharmaceutical ingredients (API). Therefore, a considerable interest has arisen in pharmaceutical companies in chiral separations in order to eliminate the unwanted isomer. The most frequently used method for chiral separations is the so-called classical resolution method, which involves formation of diastereoisomeric salts. The diastereoisomers are then separated by conventional crystallization. The efficiency of the operation is determined by the solid phase behavior of chiral systems. The separation is the most challenging when solid solutions are formed, which occurs for components with miscibility in the solid phase.[1]

**2. Methods**

Two different model systems were analysed, which consisted of pharmaceutically active stereoisomers that showed miscibility in the solid phase: System I, which was a mixture of diastereoisomeric salts of citalopram with (+)-O,O′-di-p-toluoyl-D-tartaric acid, ((+)DTT)), and System II, which was a mixture of stereoisomeric salts of nafronyl with oxalic acid. The nafronyl molecule possesses two stereogenic centers.

**3. Results and discussion**

The solid-liquid equilibrium (SLE) data acquired for System I are presented in Fig. 1A. It is evident that the solubility of S-citalopram·(+)DTT is higher compared to R-citalopram·(+)DTT, therefore, the former can be enriched in the mother liquor. The SLE data indicate the formation of solid solutions in the crystalline phase. The equilibrium relationship for the mixture of nafronyl oxalate stereoisomers in System II is much more complex (Fig. 1B), particularly in case of the dependency, for which the equilibrium curve consists of the upward and downward sloping parts. The composition region, in which the same liquid concentration can be matched with

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The composition region, in which the same liquid concentration can be matched with more than one equilibrium concentration in the solid phase indicates the possibility of establishing multiple equilibrium states.[2]

**Figure 1.**Characterization of SLE for *System* I (A), *System* II (B). Symbols – exp. data, lines - polynomial approx.

This phenomenon can be most probably attributed to polymorphic behaviour of one component showing also miscibility at the solid state.

The crystallization kinetics for System I were measured for different compositions diastereoisomeric mixtures of S- and R-citalopram·(+)DTT. The experiments were performed for the seeded and unseeded solutions. From Fig. 2. A it can be observed that the process can be accelerated by seeding the solutions. In case of the seeded crystallization, the concentration drop in the mother liquor is almost instantaneous, while it is delayed for the unseeded one. This indicates that nucleation is the rate limiting step of the operation.

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**Figure 2.**Course of the crystallization for seeded and unseeded solutions in: A) *System* I, B) *System* II [3]

The crystallization kinetics for System II were measured for the mixtures of two racemates 2,4 and 1,3. To determine the impact of seeding on both the process kinetics and the phase behavior, the seeded and unseeded crystallizations were performed in parallel for solid mixtures with the feed composition in the range corresponding to the occurrence of dual equilibrium states (hatched area in Fig. 1B). The seeded crystallization was markedly faster than the unseeded one (Fig. 2B), and the composition of seeds determined the course of the process and the equilibrium state (curves 1,2,3 in Fig. 2B), therefore, the course of the crystallization and the occurrence of the desired state could be imposed by addition of seeds with appropriate composition. When no seeds were added, the equilibrium states corresponding to the left-hand side or right hand-side of the equilibrium curve for racemate 1,3 (Fig. 1B) were established randomly (Fig. 2B). This behavior could be attributed to the co-existence of different polymorphs, which both formed solid solutions but with different solid phase compositions.

To describe the crystallization kinetics, a mathematical model was developed based on the moment method. The model accounted for cooperative nucleation and crystal growth in the solid solution forming system. The model was efficient in reproducing the kinetic profiles in the seeded as well as unseeded crystallization in both systems. Typical results of the model simulations are compared to the experimental data in Fig. 2.

**4. Conclusions**

Both Systems I and II differed in phase behavior; in the former the target compound was enriched in the mother liquor, whereas in the latter one in the crystalline phase. In System I the equilibrium states were established reproducibly regardless of the composition of the mixture, whereas in System II multiple equilibrium states were established, which most probably was caused by the formation of polymorphs. The mathematical model developed can potentially be used for description of crystallization kinetics in other solid solution forming systems.

**References**

1. H. Lorenz, A. Seidel-Morgenstern, Angew. Chem., Int. Ed. **53** (2014) 1218 – 1250.
2. Balawejder M., Mossety-Leszczak B., Poplewska I., Lorenz H., Seidel-Morgenstern A., Piątkowski W., Antos D., Fluid Phase Eq., **346** (2013), 8–19.
3. M. Olbrycht, D. Kiwala, M. Balawejder, A. Seidel-Morgenstern, W. Piątkowski, D. Antos, Cryst. Growth Des. **16** (2016) 5049−5058.
4. M. Olbrycht, M. Balawejder, I. Poplewska, H. Lorenz, A. Seidel-Morgenstern, W. Piątkowski, D. Antos, Cryst. Growth Des., just accepted, 10 January (2019), DOI: 10.1021/acs.cgd.8b01768.

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