Application of Direct Crystallization for Racemic Compound Propranolol Hydrochloride

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ABSTRACT: The application of direct crystallization integrating with chromatography to the resolution of a racemic compound propranolol hydrochloride was studied and the crystallization progression was clearly illustrated in terms of the diagram of solubility and metastable zone widths with different enantiomeric compositions. The solubility and metastable zone widths of propranolol hydrochloride in the mixture of methanol and isopropanol were determined using an *in situ* Lasentec Focused Beam Reflectance Measurement (FBRM) probe. The direct crystallizations were carried out in an automatic lab reactor (Mettler Toledo LabMax) system. The optical purity of final product crystals was examined using differential scanning calorimetry (DSC), HPLC and PXRD. The crystal size distribution and morphology were analyzed using Malvern Mastersizer and Jeol SEM. It was found that optically pure crystal product could be obtained within certain safe supersaturation limit and there was no evidence of polymorph or solvate/hydrate transformation during the crystallization process. There was no selectivity of crystal growth or nucleation between the pure enantiomer and its racemate when the solution reaches the temperature lower than saturation temperature of the racemate. Hence, the critical supersaturation control of a solution was essential to obtain pure enantiomers from a partially resolved racemate. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 96:2735–2745, 2007

Keywords: direct crystallization; racemic compound; solubility; metastable zone width; HPLC; optical purity; DSC; FBRM

INTRODUCTION

Crystallization techniques provide powerful aids in the production of single-enantiomer products, which are of particular importance in the manufacture of chiral drugs. The application of direct crystallization (preferential crystallization) in the resolution of a racemic conglomerate has been widely studied.[1–8] With the big progress made in the field of asymmetric synthesis and SMB chromatography, etc.[9–13] the partially resolved racemic compounds are easily available. However, these samples are often highly diluted and the enantiomeric purity is insufficient. In addition, it would require much more extra efforts to acquire an optically pure product rather than a partially resolved sample using asymmetric synthesis or SMB alone. In this case, direct crystallization can be applied to further purify the partially resolved samples. In the aspects of low cost and advantages of solid product, direct crystallization also shows big advantages for the enrichment of chiral compounds.[10,14]

However, there is few commercial precedents of a direct crystallization process for chiral materials, due to a number of difficulties, such as the fewer cases of racemic conglomerate forming

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systems in the family of chiral compounds and crucial properties of racemic compound forming systems as well as lack of knowledge of precisely *in situ* monitoring and controlling the critical properties of crystallization processes. Our group has recently developed a systematic approach to investigate preferential crystallization by integration of system thermodynamics, crystallization kinetics, optimal operation and *in situ* monitoring.[8] The present work is to extend this systematic approach to explore the application of direct crystallization to racemic compound coupling with chromatography.

The feasibility and yield of pure enantiomer obtainable by direct crystallization is determined by the characteristics of the phase diagrams (binary or ternary phase diagram) of the system and the initial enantiomeric composition of the feed to the crystallizer.[1–3,10] For a racemic compound, three possible situations are illustrated in Figure 1. It shows that the knowledge of the phase equilibria is even more important for a racemic compound because the existence region of the pure enantiomers in the phase diagram, which is defined by the position of the ternary eutectic point, in most cases, is much smaller than a racemic conglomerate. A pure enantiomer can only be produced by direct crystallization when the initial solution composition is located inside the existence region of the pure enantiomers covered by AED or A'E'L. In the most favorable case, as shown in Figure 1(c), the racemic compound exhibits an ideal phase diagram with the maximum operating region to obtain pure enantiomers by crystallization. In the case of a combined process of chromatography and crystallization, the previous chromatographic step must deliver a minimum enantiomeric enrichment which exceeds that of the eutectic point in the ternary phase diagram. Subsequently, the resulting highly diluted and undersaturated solution has to be concentrated to reach a composition in the pure enantiomer existence region to gain a pure enantiomer by following crystallization step.

Propranolol hydrochloride,[15–21] as shown in Figure 2, is a synthetic beta-adrenergic receptor blocking agent widely used in the treatment of hypertension. Although it is administrated as the racemate form, only (*S*)-enantiomer has the desired beta-adrenergic blocking effect. In the previous work,[19–21] it was identified as a racemic compound forming system.

The ternary phase diagram of propranolol hydrochloride dissolved in the mixture of methanol and isopropanol (Fig. 4) has the most favorable shape as shown in Figure 1(c) for obtaining the pure enantiomer by direct crystallization. The mixture having the eutectic composition is the racemate. The racemate can be readily separated by chromatography.[22,23] Furthermore, the two pure enantiomers are commercially available at a reasonable price. Therefore, propranolol hydrochloride dissolved in the mixture of methanol and isopropanol was chosen as a suitable model system to explore the combination of chromatographic and crystallization separation techniques.

The resolution of propranolol hydrochloride via chromatography with analytical column has been reported by Ching et al.[22] and Ng et al.[23] However, the mechanism of crystallization process for propranolol hydrochloride, which is a racemic compound, has been rarely investigated. This work presents such an effort to obtain a certain enantiomerically enriched propranolol hydrochloride starting from a racemic composition using a HPLC with a semi-preparative chiral column. A subsequent systematical study of direct crystallization process starting from the same

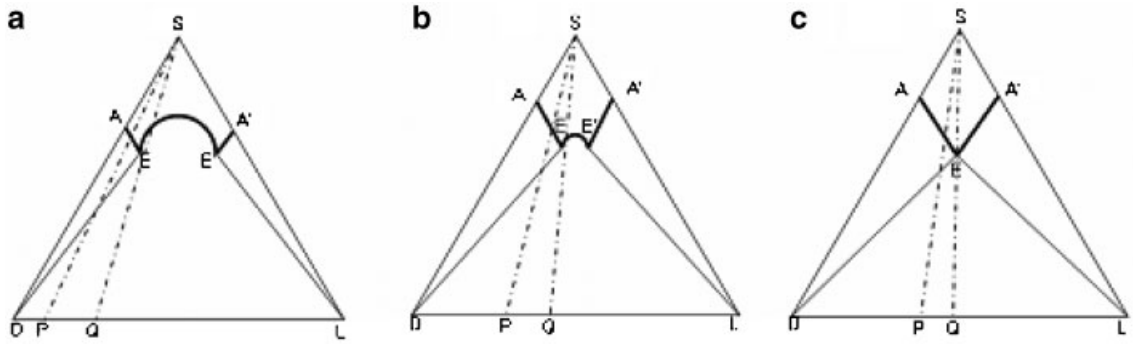

Figure 1. Ternary phase diagrams for a racemic compound: (a) unfavorable; (b) more favorable; (c) most favourable.