Identification and Characterization of Solid-State Nature of 2-Chloromandelic Acid

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ABSTRACT: The racemate and enantiomers of 2-chloromandelic acid were characterized by SS-NMR, XRPD, and FTIR. The binary melting point phase diagram was constructed by DSC (differential scanning calorimetry). The solid-state nature of 2-chloromandelic acid was identified to be a racemic compound. The crystal structure of racemic compound was determined to be monoclinic $P2_1/c$. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:1835–1844, 2009
Keywords: 2-chloromandelic acid; racemate; enantiomer; conglomerate; differential scanning calorimetry; melting point diagram; crystal structure

INTRODUCTION

In 1992, FDA released the new guidelines that no racemates are allowed to enter the market as new medicines[1] which resulted in a world-wide accelerating effort by pharmaceutical companies for developing new chiral drugs and meanwhile substituting the marketed drugs in racemate form by pure enantiomers. Nowadays, more than half of all marketed drugs are chiral[2] and 9 out of the top 10 drugs have chiral active ingredients.[3]

The increasing demand of chiral drugs has dramatically prompted the development of more efficient preparation methods. To date, the asymmetric synthesis, crystallization resolution, enzymatic resolutions and chiral chromatography separation are the main available preparation methods. Although asymmetric synthesis, enzymatic resolutions and chiral chromatography separation have advanced steadily, until now, resolution by crystallization remains an important and the most economic process for industrial scale production.[4] However, for some racemates, to achieve high optical purity enantiomers, several recrystallizaitons have to be performed. Large amount of solvent and laborious steps make the cost increase sharply. Thus, coupling hybrid separation process with crystallization was attempted to improve the separation efficiency.[5,6]

In chiral resolution using crystallization or a hybrid of crystallization with other separation processes, determination of the solid nature of racemate is of great significance. It is the prerequisite for rational design of resolution and purification process. The racemate is generally classified into conglomerate, racemic compound and pseudoracemate (solid solution). Conglomerate is a physical mixture of equal molar homochrial crystal which only contains one kind of enantiomer. Racemic compound consists of heterochiral crystals in which two enantiomers coexist orderly in one unit cell. Pseudoracemate is a homogenous solid solution containing equal amounts of two enantiomers unordered in the

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crystal lattice. The characteristic binary diagrams are depicted in Figure 1, respectively. Separation using preferential crystallization without any chiral selector is applied for the case of conglomerates while diastereomeric salt formation is employed for racemic compounds and pseudoracemates.[7] In addition, final crystallization is also required to arrive at desired solid state form and desired purity.[8]

Construction of a binary diagram by measuring melting behavior of the mixtures corresponding to different enantiomeric composition has been traditionally used to identify the solid state nature of the racemate. However, only constructing the binary diagram alone is not enough in some cases when racemate can exist as metastable solid state. The comparison of structural difference between enantiomers and racemate can also be made using X-ray diffraction patterns, solid-state nuclear magnetic resonance (NMR) and solid-state FTIR spectroscopy.[9–12] More often, the binary diagram of racemate does not exist as one of the three fundamental types shown in Figure 1. They may exist as conglomerate and racemic compound with partial solid solution as shown in Figure 2 or more complicated binary diagrams identified first by Roozeboom.[7,13,14] This makes the identification of racemates quite a challenging task. Therefore, binary diagram, solid-state spectroscopic patterns and theoretical thermodynamic calculation have to be examined comprehensively and critically to avoid leading to erroneous results.

Mandelic acid analogues are important pharmacuetical intermediates and are frequently used

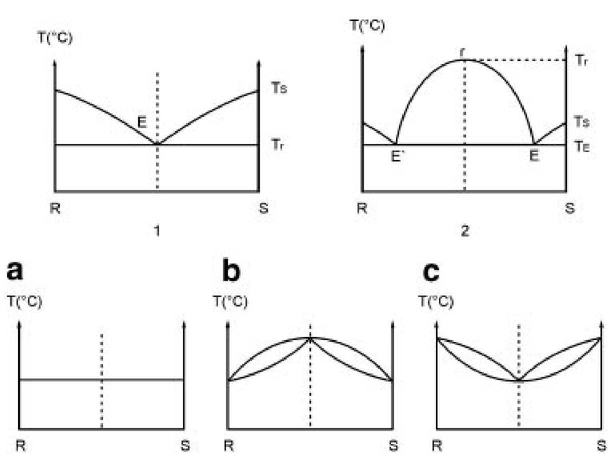

Figure 1. Typical binary phase diagrams of racemate, 1, Conglomerate system; 2, Racemic compound system; 3, Pseudoracemate system: (a–c) three types of pseudoracemate. Reprinted from Ref. 8.

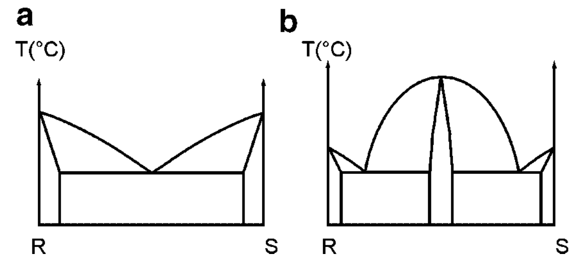

Figure 2. Conglomerate and racemic compounds with partial solid solutions: (a) the partial solid solution in the vicinity of pure enantiomer, (b) the partial solid solution in the vicinity of both pure enantiomer and racemic compound. Reprinted from Ref. 8.

as resolving agents. Investigation of their binary phase diagram could provide a rational basis for chiral separation. Some previous works have focused on mandelic acid system.[15,16] However, to the best of our knowledge, there is no report on binary diagram of 2-chloromandelic acid (hereafter 2-ClMA, $C_8H_7O_3Cl$, structure is illustrated in Fig. 3). R-2-chloromandelic acid (hereafter R-2-ClMA) is a key intermediate for the production of Clopidogrel, a widely administered anticoagulant that can reduce the risk of cardiovascular failures in patients with acute coronary syndromes.[17,18] Besides, it is also an important resolving agent in chiral resolution processes. Therefore, numerous efforts have been made in past two decades to develop efficient preparation methods for R-2-CLMA including diastereomeric salt resolution, enzymatic resolution, and asymmetric synthesis.[19–22] However, each method has its limitations, such as the high cost of the chiral agent, many separation steps, or low optical purity.

During our resolution work, we noticed that the difference between the melting points of racemate of 2-chloromandelic acid (90.3°C) and the corresponding pure enatiomer (118.7°C) is nearly −30°C. The difference of enthalpy of fusion of racemate and enantiomer is −9.66 J/g which suggests that the racemate is more likely a conglomerate.[4,7] If this system were conglomerate, the preferential crystallization which does not

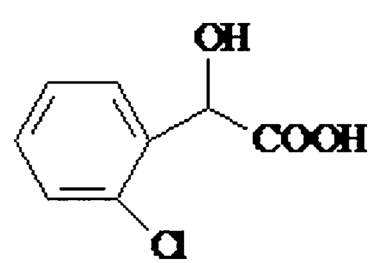

Figure 3. Formula of 2-chloromandelic acid.

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