Complementary Crystallography and X-ray Powder Diffraction Methods

Greg Stephenson
Research Advisor
Eli Lilly and Company
Preformulations
Solid-State Pharmaceutics

Identify a phase that is suitable for a product

“Safe and Efficacious”

Bioavailable – sufficiently soluble to achieve efficacy

Physically and Chemically Stable no-phase transitions and less than 2% decomposition when stored for 2 years with 5 to 10 other excipients and exposed to 20-75%RH

Crystalline, Soluble, Non-solvated, filters well, non-hygroscopic, is flowable…..is that all?……um…with just 2g of material in less than 30 days?
Non-discrete phases (continuous)

In that quest – we find many phases that are not discrete

    Iso-structural Solvates: drug packs in the same arrangement in the
    crystal lattice with many different solvents

    (or Iso-structural desolvates or “variable hydrates”)

Less commonly Iso-structural Salts

and Solid-Solutions

Also talk about:

Discuss a couple of Discrete Phases, one quite interesting

End with a Structure solution from Powder Diffraction
Erythromycin Dihydrate: Same or Different Form Based on X-ray Powder Diffraction?
Molecular Structures of Erythromycin A and Erythromycin B

Erythromycin B lacks hydroxyl group
Erythromycin A and Erythromycin B Dihydrate Crystal Forms

Isostructural Dihydrates

Erythromycin A dihydrate
Orthorhombic, S.G. P 2₁ 2₁ 2₁
a = 9.1829(8) Å
b = 9.6316(7) Å
c = 47.151(13) Å

Erythromycin B dihydrate
Orthorhombic, S.G. P 2₁ 2₁ 2₁
a = 9.170(1) Å
b = 9.672(1) Å
c = 46.985(1) Å

J.Pharm.Sci. (1997), 86, 1239. CCDC Ref Code NAVTA and NAVTEJ
Erythromycin A dihydrate versus Erythromycin B dihydrate
Different

Unit cell metrics nearly identical
Unit cell contents nearly identical
Molecular Packing nearly identical
Much information in a Thermal Ellipsoid diagram

Something Wrong with Hydroxyl group during refinement
Refine Hydroxyl Group Site Occupancy

This is actually a solid solution formed upon crystallization of the two molecule's

38% Erythromycin A, 62% Erythromycin B
Well Behaved Structure
(Thermal ellipsoid plot)

All atoms have similar thermal parameters other than where expected
Solid-Solution Formation, Reasonably Common with Related Substances or Natural Products

Solid-Solutions are reasonably common, however are often overlooked

Commonly found in crystallization processes
  • That related substance that you just can’t seem to reject

Need to find conditions that result in phase separation
  • Screen for a solvent that results in different crystal forms for the two different substances, those conditions should afford separation
Coefficient of Isomorphism

Kitaigorodskii defines a coefficient of isosterism - compares molecular volumes common to two molecules that are arranged in such a fashion as to maximize the superposition of constituent groups

\[ \epsilon = 1 - \left( \frac{V_{no-overlap}}{V_{overlap}} \right) \]

No solid solution is likely to form when \( < 0.8 \), but is likely when \( > 0.9 \)

Hence larger molecules and related substances

Crystallization of Racemic Compounds

Solution of Two Enantiomers

~90% of the time

~10% of the time

Wallach’s Rule\(^1\) states that racemic crystals tend to be denser than their chiral counterparts


Racemic Crystals

Mixture of Chiral Crystals of Opposite “Handedness” Conglomerate Mixture
Analytical Differentiation of Racemic Crystals versus a Conglomerate

Racemic Crystals

Single Crystals Method

Structure (molecular arrangement) differs from Chiral Forms

Chiral Crystals

Same Crystal Packing, however Mirror Image Structures

Powder Diffraction (ssNMR, IR, Raman, mp)
Racemic Ibuprofen and its S Enantiomer

Monoclinic Space Group \( P2_1/c \)
\[ a = 14.67 \, \text{Å} \quad b = 7.89 \, \text{Å} \quad c = 10.73 \, \text{Å} \]
Beta = 99.43°

Monoclinic Space Group \( P2_1 \)
\[ a = 12.46 \, \text{Å} \quad b = 8.08 \, \text{Å} \quad c = 13.54 \, \text{Å} \]
Beta = 112.89°

CCDC Structure COTYOA01K.H.Stone, S.Lapidus, P.W.Stephens

CCDC Structure JEKNOC10
A.A.Freer, J.M.Bunyan, N.Shankland, D.B.Sheen
Racemic Crystal Versus Enantiomer

![Graph showing the comparison between Racemic Ibuprofen and S-Ibuprofen](image)
Phase Diagram of Solid Solution

Figure 1. Binary phase diagram of enantiomer mixtures forming (a) a conglomerate, (b) a racemic compound, and (c) a solid solution. $^2 R$, $S$, $RS$, and $L$ represent respectively solid $R$-enantiomer phase, solid $S$-enantiomer phase, racemic compound $RS$, or solid solution $RS$ and liquid phase.

Atenolol
Racemate versus Enantiomer


(RS)-Atenolol
C 2/c
a = 55.83(3) Å  b = 5.559(3) Å  c = 9.734(2) Å
α = 90°  β = 100.042(6)°  γ = 90°
Volume = 2974.75 Å/cm³
Z: 8  Z': 1

(S)-Atenolol
C 2
a = 54.43(3) Å  b = 5.712(3) Å  c = 9.676(2) Å
α = 90°  β = 99.510(6)°  γ = 90°
Volume = 2966.96 Å/cm³
Z: 8  Z': 2
Chiral Structure Disordered “Pseudo-Symmetry”

(RS)-Atenolol
C 2/c
\[ a = 55.83(3)\text{Å} \quad b = 5.559(3)\text{Å} \quad c = 9.734(2)\text{Å} \]
\[ \alpha = 90^\circ \quad \beta = 100.042(6)^\circ \quad \gamma = 90^\circ \]
Volume = 2974.75 Å/cm³
Z: 8 Z': 1

(S)-Atenolol
C 2
\[ a = 54.43(3)\text{Å} \quad b = 5.712(3)\text{Å} \quad c = 9.676(2)\text{Å} \]
\[ \alpha = 90^\circ \quad \beta = 99.510(6)^\circ \quad \gamma = 90^\circ \]
Volume = 2966.96 Å/cm³
Z: 8 Z': 2
Phase Diagram of Solid Solution

Figure 1. Binary phase diagram of enantiomer mixtures forming (a) a conglomerate, (b) a racemic compound, and (c) a solid solution.\textsuperscript{2} \( R, S, RS, \) and \( L \) represent respectively solid \( R \)-enantiomer phase, solid \( S \)-enantiomer phase, racemic compound \( RS \), or solid solution \( RS \) and liquid phase.

Racemic or Conglomerate?

Racemic Material
(Chiral LC 50%R/50%S)

Chiral Purity > 98%
Chiral vs Racemic Crystals: Unit Cells

Enantiomer: Orthorhombic $\text{P}2_1\text{2}_1\text{2}_1$
$\begin{align*}
a &= 4.97 \text{ Å}, \\
b &= 15.50 \text{ Å}, \\
c &= 17.96 \text{ Å}
\end{align*}$

Volume = 1383.64 Å$^3$, $Z=4$, $Z'=1$, density = 1.348 g/cc
Enthalpy of Fusion 99.43 J/g, Tm 127.16°C

Racemate: Monoclinic $\text{P}2_1/c$
$\begin{align*}
a &= 4.94 \text{ Å}, \\
b &= 18.14 \text{ Å}, \\
c &= 15.61 \text{ Å} \\
\beta &= 92.951°
\end{align*}$

Volume = 1395.90 Å$^3$, $Z = 4$, $Z' = 1$, density = 1.336 g/cc
Enthalpy of Fusion 102.19 J/g, Tm 136.09°C
Looking at Super Structure

Chiral, Enantiopure
P2₁2₁2₁

Racemic, both enantiomers present in unit cell
P2₁/c
A Closer Look
Truly Racemic Crystal Not a Solid Solution Confirmed by Thermal Analysis

Figure 1. Binary phase diagram of enantiomer mixtures forming (a) a conglomerate, (b) a racemic compound, and (c) a solid solution. R, S, RS, and L represent respectively solid R-enantiomer phase, solid S-enantiomer phase, racemic compound RS, or solid solution RS and liquid phase.
Phase Diagram of Enantiomeric Mixtures

The phase diagram for a mixture of two enantiomers can be calculated using the Schroder Van-Laar equation to determine the liquidus curve for the portion of the phase diagram which is at the extremes of chiral purity as expressed below:

Equation. 1 \[ \ln x = \Delta H_f^A / R \left( 1/T_f^A - 1/T \right) \]

where \( R = 1.9869 \text{ cal mol}^{-1} \text{ K}^{-1} \), \( x \) is the mole fraction of the more abundant enantiomer \((0.5 \leq x \leq 1)\) of a mixture whose melting terminates at \( T \) (degrees K). \( \Delta H_f^A \) and \( T_f^A \) are the enthalpy of fusion and the melting point of the pure enantiomer. Usually these curves are symmetrical at the two extremes. In the case of LY356735 versus LY356736, the enantiomerically pure regions are not the same, since the stable form of LY356736 is the more stable crystalline form, whereas the form used for LY356735 is the metastable polymorphic form. The two polymorphs have different melting points and enthalpies of fusion, hence the curves are not symmetrical.

The Prigogine and Defay equation can be used for calculating the liquidus curve for the racemic portion of the curve (from \( x=0.5 \) to where the mole fraction defines the two eutectic points) as define below:

Eqn. 2 \[ \ln 4x (1-x) = 2 \Delta H_f^R / R \left( 1/T_f^R - 1/T \right) \]

The same variables are used, however the enthalpy of fusion, \( \Delta H_f^R \), of the racemate and the temperature of melting of the racemic crystal, \( T_f^R \), is used throughout this region of the phase diagram.

Experimental data was collected at 10 percent intervals and was used to validate the calculations.