



How to obtain enantiopure drug substance through crystallization?



Chirality is defined as the geometric property of an object, like a molecule, of not being superimposable with its mirror image. The two mirror images of a chiral molecule are called enantiomers. Enantiomers have essentially identical physical and chemical properties. However, in chiral environments, such as the receptors and enzymes in the body, enantiomers may behave differently and therefore exhibit different pharmacokinetic properties and exert quantitatively or qualitatively different pharmacological or toxicological effects.

Chemical synthesis of chiral molecules usually delivers a racemic mixture, i.e. a 50:50 mixture of two enantiomers. In the past, chiral drugs were usually developed as racemic mixtures since separation into the individual enantiomers was technically difficult to achieve. However, technological advances have opened up the possibility of producing single enantiomers on large scale. Since the development of racemic mixtures raises issues of acceptable manufacturing control and adequate pharmacologic and toxicologic assessment, it has become common practice to develop chiral drugs as single enantiomers rather than as racemic mixtures.

The development of procedures to obtain single enantiomers therefore constitute an important component of contemporary development programs for chiral drug substances. Essentially, enantiopure drug substance may be obtained in three ways, namely through separation, asymmetric synthesis or chiral crystallization. Chiral crystallization is an attractive approach in early development, as it is cost-effective, broadly applicable and easily scaled up.

Chiral resolution through crystallization may be achieved in several ways. One technique is conversion of the enantiomeric substance into a diastereomeric salt (diastereomeric resolution). Diastereomers are substances that contain more than one chiral center and are not mirror images of one another. They therefore exhibit different physical-chemical properties, which opens up the possibility of selectively crystallizing a chirally pure form from a racemic mixture. For this technique to work, the drug substance should have an acidic or basic functional group to enable salt formation.



Chiral crystallization techniques

Method	Prerequisites	Maximum Yield
Diastereomeric resolution	Diastereomeric salt can be formed	50%
Preferential crystallization	Conglomerate solid or salt can be formed	50%
Viedma ripening & Thermocycling	Conglomerate solid + solution racemization	100%
Crystallization-Induced Diastereomer Transformation	Diastereomeric solid + solution racemization	100%

Another crystallization approach to obtaining enantiopure product is conglomerate formation. A conglomerate species exhibits complete chiral discrimination in the crystalline state. This property may be harnessed to isolate enantiopure product through preferential crystallization. The chance of identifying a conglomerate-forming solid form increases with polymorphicity. The yield of enantiopure drug substance obtained using diastereomeric resolution and preferential crystallization is inherently limited to 50%. However, for compounds that can undergo racemization (i.e., repeatedly convert into the other enantiomer) in solution, higher yields may be obtained. For example, a molecule with an acidic chiral center may undergo solution racemization using a base as a catalyst. Through judicious combination of conglomerate formation and solution racemization, complete deracemization (100% chiral purity, 100% yield) may be achieved. Examples of such procedures include Viedma ripening (grinding of a suspension) or thermocycling. The identification of suitable diastereomeric salts or conglomerates requires extensive experimentation (for instance, it is estimated that less than 10% of chiral compounds crystallize as conglomerates), and is therefore best achieved via miniaturized, high-throughput screening setups. Our approach at Ardena generally consists of:

A primary screen using high-throughput X-ray powder diffraction (XRPD) as analytical tool
Physicochemical characterization of screening hits via high-resolution XRPD, differential scanning calorimetry, thermo-gravimetric analysis and dynamic vapor sorption
scale parallel crystallizers to determine the conditions that deliver the desired chiral form in high yield and high enantiomeric excess
Process development at scale in the pilot plant

