Ardena Insight

Chirality in drug development: from racemic mixtures to enantiopure substances

Chirality is defined as the geometric property of an object, such as a molecule, that is not superimposable on 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 with a single chiral center 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 scalable.

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 stereoisomers that are not mirror images of one another, and typically exhibit different physical-chemical properties. This difference opens up the possibility of selectively crystallizing a chirally pure form from a racemic mixture. For this technique to work, the drug substance must have an acidic or basic functional group to enable salt formation.

Method	Prerequisites	Maximun Yield
Diastereomeric resolution	**Diastereomeric salt can be formed**	**50%**
Prefential 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%**

▲ Chiral crystallization techniques

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 likelihood of identifying a conglomerate-forming solid form increases with polymorphicity. The yield of enantiopure drug substance obtained using diastereomeric resolution and preferential crystallization is tipically limited to 50%. However, for compounds that can undergo racemization (i.e., interconversion 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.

At Ardena, our approach generally consists of:

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