

Process Strategies for Batch Preferential Crystallization

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Abstract

An abundance of molecules belongs to the class of chiral compounds that exist in two possible three-dimensional mirrored conformations (enantiomers). Apart from the spatial arrangement they are virtually identical sharing the same physical and chemical properties. Over the course of evolution, nature eventually favored one of two enantiomers of a molecule to build living organisms. This is commonly referred to as homochirality of life. As a consequence, every biological entity is capable to distinguish between enantiomers. This can have fatal consequences especially when chiral molecules are used in pharmaceutical drugs. The most prominent example for such a failure was the thalidomide tragedy, which led to the insight that chiral active pharmaceutical ingredients have to be provided as single enantiomers and not as a 50:50 mixture (racemate). Access is, however, complicated by their identity. It is possible to selectively synthesize one enantiomer by chemical means with significant effort. In many cases the final product has to be in the solid state though requiring additional steps such as crystallization or precipitation.

An alternative strategy is the separation of the racemate. Apart from chromatography, which results in a highly pure but very dilute product stream, crystallization is an attractive process combining separation and solid formation in one step. The enantiomers of a certain class of chiral molecules can be separated by so-called preferential crystallization. This technique allows direct crystallization of single enantiomers from a racemic solution.

The focus of this work is a systematic experimental and theoretical investigation of preferential crystallization. The aim is to increase robustness and yield as well as the optimization of process conditions, which involves the study of novel operating modes.

Kurzreferat

Eine Vielzahl an Molekülen gehört zu der Klasse chiraler Verbindungen, die sich dadurch auszeichnen, dass es jeweils zwei räumliche Anordnungen gibt, die spiegelbildlich zueinander sind. Es handelt sich daher um praktisch identische Moleküle (Enantiomere), die sich lediglich in der dreidimensionalen Anordnung der Atome unterscheiden, ansonsten aber identische physikalische und chemische Eigenschaften besitzen. Im Laufe der Evolution hat sich die Natur bei der Entstehung lebender Organismen letztendlich für eines der möglichen Enantiomere eines solchen chiralen Moleküls entschieden, was gemeinhin als Homochiralität des Lebens bezeichnet wird. Aus diesem Grund sind jegliche biologischen Organismen, so auch der Mensch, in der Lage zwischen Enantiomeren zu unterscheiden. Dies kann fatale Folgen haben, wenn es sich bei den Molekülen um pharmazeutisch aktive Substanzen handelt, wie es bei dem Medikament Thalidomid (Contergan) der Fall war. Es ist daher vor allem in der Pharmaindustrie notwendig reine Enantiomere, anstelle von 50:50 Gemischen beider Moleküle (Racemate) zu verwenden. Der Zugang gestaltet sich aufgrund der Ähnlichkeit jedoch als schwierig. Auf chemischem Weg ist es mit beträchtlichem Aufwand möglich, eines der beiden Spiegelbilder selektiv zu synthetisieren. Letztendlich soll jedoch das Endprodukt

häufig als Feststoff zur weiteren Verarbeitung vorliegen, weshalb zusätzliche Prozessschritte, wie Kristallisation oder Fällung notwendig sind.

Alternativ zur selektiven Synthese reiner Enantiomere gibt es die Möglichkeit, das Racemat durch Trennverfahren zu spalten. Neben der Chromatografie, die zunächst ein hochreines aber stark verdünntes gelöstes Produkt erzeugt, gibt es Kristallisationsverfahren, die in der Lage sind Trennung und Feststoffbildung in einem Prozessschritt zu vereinen. Für eine bestimmte Klasse chiraler Moleküle kann die sogenannte bevorzugte Kristallisation verwendet werden, mit der es möglich ist, aus einer übersättigten racemischen Lösung reines Enantiomer in kristalliner Form zu gewinnen.

Die bevorzugte Kristallisation ist Gegenstand der vorliegenden Arbeit. Im Vordergrund systematischer experimenteller und theoretischer Studien stehen dabei die Erhöhung der Robustheit und Ausbeute, die Optimierung der Prozessbedingungen, sowie die Untersuchung neuartiger Betriebsweisen.

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