Engineered crystals as a Racemate-to-Homochiral approach: chirality manipulation towards chiral resolution and the design of novel solid forms.

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Crystal engineering (CE) has been a remarkable tool for obtaining and improving the physicochemical properties of a compound [1]. However, for racemic systems, the selectivity and specificity of the enantiomers challenge the design of molecular crystals. In particular the variability of solid forms that chirality implies, i. e. racemates, conglomerates, or solid solutions [2] are frequently unpredictable, as is the outcome of any crystallization. In the pharmaceutical context, in particular, several pharmaceutical compounds are still being delivered as racemates. There is a scientific and pharmaceutical demand for efficient and lower-cost resolution methods [3, 4]. To overcome this, we propose a crystal engineering approach (salt formation, cocrystallization, *etc*.) for the development of enantiomeric resolution protocols for selected pharmaceutical compounds. Although racemates are a recurrent response [2], the formation of conglomerates can be CE designed by selecting a suitable agent, which forms H-bonds selectively with one enantiomer forming homochiral arrangements. Thus, the study of selection, preparation and analysis of multi-component crystals (MCC) has been the first part of this investigation. The compounds Carvedilol, Atenolol and Propranolol are important β-blocker drugs delivered at racemic mixtures of R and S enantiomers. Their structures feature polar groups that are adjacent and directly attached to the asymmetric carbon. The antidepressants Bupropion, Fluoxetine and Citalopram show enantiomers with molecular structures in which the chiral center does not have polar groups. The antimalarial Mefloquine is a racemic compound in which the enantiomers comprise two asymmetric carbons and it is marketed as a mixture of (R,S) and (S,R) enantiomers. Considering these structural features and the pharmaceutical relevance, these racemic active pharmaceutical ingredients have been chosen as model compounds for this study. MCC of these compounds have been screened using the CE techniques, crystallization from the melt and mechanochemistry, and can point towards a resolution process via crystallization. Finally, this opens a perspective for the formation of materials with different properties and applications, as well as for the correlation between supramolecular recognition and resolution protocols.

[1] G. R. Desiraju. Crystal engineering: A brief overview. J. Chem. Sci., 122, 667-675 (2010).
[2] J. Jacques, A. Collet, S. H. Wilen. Enantiomers, racemates, and resolutions, Krieger Pub. Co., (1994).
[3] Blaser, H.-U., Chirality and its implications for the pharmaceutical industry. Rendiconti Lincei, 24, 3, 213-216 (2013).
[4] Calcaterra, A.; D'Acquarica, I., The market of chiral drugs: Chiral switches versus de novo enantiomerically pure compounds. J. Pharm. Biomed. Anal., 147, 323-340 (2018).

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