Multicomponent Design to Unlock New Opportunities for Topical Drugs

Joana F. C. Silva,[1] Markus von Raumer,[2] T. Wedel.[1]

[1]Corden Pharma Switzerland LLC, Eichenweg 1, 4410 Liestal, Switzerland.
[2]Corden Pharma International Switzerland LLC, Aeschenvorstadt 71, 4051 Basel, Switzerland.
joana.silva@cordenpharma.com

Most active pharmaceutical ingredients (APIs) are developed and manufactured as crystalline solids. While solid-form control is well-established for oral drug products, the growing use of advanced dosage forms requires broader application of crystal engineering principles to optimize manufacturability and performance across different delivery routes.[1]

In topical drug products, skin penetration is a major barrier to efficacy, and only small molecules with a balanced lipophilicity and sufficient aqueous solubility can effectively permeate the skin.[2] Clotrimazole (CTZ) is an imidazole derivative widely used in topical formulations. It is classified as a BCS class II drug, characterized by high lipophilicity and poor aqueous solubility.[3] Although its intrinsic permeability is favorable, limited water solubility may reduce the amount available for skin absorption. By modifying the intermolecular interactions without changing the drug molecule, cocrystals can produce new solid forms with improved performance potential and broader formulation opportunities.[4]

The clotrimazole-hydroquinone (HQN) system was selected to illustrate a rational approach to multicomponent solid-form design. Two distinct cocrystals with 2:1 and 1:1 CTZ-HQN stoichiometries were successfully obtained through mechanochemical and solution-based methods, and their structural and thermal properties were characterized using XRPD, FTIR-ATR and DSC. Construction of the binary solid-liquid phase diagram enabled assessment of the thermodynamic relationships between the two cocrystals and their pure components, revealing multiple eutectic equilibria and competition between alternative supramolecular arrangements.

These results support the use of cocrystallization as a rational strategy to tune solid-state properties that are important for improving transdermal drug availability. Moreover, this work shows how a CDMO setting can strategically combine solid-state expertise and rapid screening to inform and accelerate formulation innovation.

[1] Gautam R. Desiraju, *Journal of the American Chemical Society*, **2013**, *135 (27),* 9952-9967.
[2] Xia-Lin Dai, Alexander P. Voronin, Yong-Liang Huang, G. L. Perlovich, Xing-Hua Zhao, Tong-Bu Lu, and Jia-Mei Chen, *Crystal Growth & Design*, **2020**, *20 (2),* 923-933.
[3] S. Blokhina, A. Sharapova, M. Ol'khovich, G. L. Perlovich, *Thermochimica Acta*, **2019**, *(682)*, 178431.
[4] Molly M. Haskins and Michael J. Zaworotko, *Crystal Growth & Design*, **2021**, *21* (7), 4141-4150.