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Mechanosynthesis of Eutectics of Anti-Inflammatory Drug Ethenzamide – A Comparison with Analogous Cocrystals

Trishna Rajbongshi,[a] Kashyap Kumar Sarmah,[b] Ramesh Ganduri,[c] Suryanarayan Cherukuvada,[c] Mihails Arhangelskis,[d] and Ranjit Thakuria*[a]

Mechanochemical milling of ethenzamide (ETZ), a nonsteroidal anti-inflammatory drug, with substituted aromatic carboxylic acids as well as anti-tuberculosis drug pyrazinamide (PZA) resulted in the formation of eutectics. Although a large number of cocrystals as well as polymorphic cocrystals are reported for ETZ, for the first time we have synthesized six eutectics including an instance of a drug-drug eutectic system. Supramolecular synthon energy calculations validate the formation of eutectic mixtures over cocrystals with coformers considered in our study.

1. Introduction

Co-crystallization has emerged as an alternative approach in optimizing various physicochemical properties such as solubility, dissolution rate, stability, bioavailability, etc. in the pharmaceutical industry.[1] The outcome of co-crystallization is the formation of supramolecular crystalline aggregates of two or more molecules through non-covalent interactions.[2] Unlike salt formation, co-crystallization does not rely on the presence of ionizable groups in the target molecules, making it a more general strategy for the screening of various multi-component solids. In the recent past, much attention has been focused on eutectics alongside cocrystals as new/alternative solid forms of active pharmaceutical ingredients (APIs).[1b,3] A eutectic is a multi-phasic crystalline ensemble of distinct solid-solutions as opposed to a single phase solid-solution. High thermodynamic functions of eutectics in terms of free energy, enthalpy and entropy can result in improved solubility/dissolution rate and crystalline nature can impart stability to drugs with poor physico-chemical properties.[4] Hence, better understanding of eutectics is imperative to enhance the solid form arsenal in achieving desired drug properties as well as intellectual property in drug industry. However, design and manifestation of eutectics is not straightforward similar to cocrystals. Restricted hetero-supramolecular growth is one of the essential strategies[2,3d,g,h,5] to design a eutectic which is very selective based on the presence as well as position of a hydrogen bonding functionality both in API and coformers.

Ethenzamide (ETZ) is a nonsteroidal anti-inflammatory drug used for the treatment of mild to moderate pain. It is one of the few APIs for which a large number of polymorphic cocrystals were reported in literature.[6] In an earlier report[7] we have synthesized a few cocrystals/cocrystal hydrates of ETZ with phenolic acid coformers, namely 2,4-dihydroxybenzoic acid (24DHBA), 3,5-dihydroxybenzoic acid (35DHBA) and ferulic acid (FRA) using mechanochemistry as well as solution crystallization. In this background, we selected unsubstituted aromatic carboxylic acids to design eutectics of ETZ based on the restricted hetero-supramolecular growth for combinations lacking additional/potent hydrogen bonding functionalities. In the anticipated lines, we obtained several eutectics of ETZ (see Scheme 1) using mechanochemical milling and discuss their formation in this contribution. Further, supramolecular synthon energy calculations were carried out to validate the formation of eutectics over cocrystals for combinations analogous to reported cocrystals.

Experimental Section

Materials

Ethenzamide (ETZ) and Pyrazinamide (PZA) were purchased from TCI chemicals (India) Pvt. Ltd. and used as received. All other coformers were purchased from commercial sources and used without further purification.

[a] T. Rajbongshi, Dr. R. Thakuria
Department of Chemistry
Gauhati University
781014Guwahati, Assam (India)
E-mail: ranjit.thakuria@gmail.com
[b] K. Kumar Sarmah
Department of Chemistry
Behali Degree College
Borgang, 784167 Biswanath, Assam (India)
[c] R. Ganduri, S. Cherukuvada
Solid State and Structural Chemistry Unit
Indian Institute of Science
560012 Bengaluru, (India)
[d] M. Arhangelskis
Faculty of Chemistry
University of Warsaw
1 Psteura Street, 02-093 Warsaw (Poland)

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