# Preliminary Screening for Cocrystallization of Methylxanthine Class of Drugs: Caffeine and Pentoxifylline

Aleksandar Cvetkovski, Valerio Bertolasi, Paola Gilli
Dipartimento di Scienze Chimiche e Farmaceutiche e Centro di Strutturistica Diffrattometrica,
Università di Ferrara,
Via L. Borsari 46, 44121 Ferrara.
*cvtlsn@unife.it*

Methylxanthines are a group of drugs encompassing the compounds which are purine bases widely used as drugs that improve peripheral circulation of blood vessels toward the diverse mechanisms of action (1). The very common use of caffeine and pentoxifylline in therapies, each of them combined with many other drugs and drug supplements for improving peripheral blood circulation raises the attention for screening cocrystals of these drugs (2).

During the last years, an increased interest for research in pharmaceutical cocrystals has been registered, using different strategies. A promising approach is to make use of the molecular recognition properties of the functional groups and their allocations in entire structures of the molecules which, depending on the polarity and atom's electronegativity, are linked one to another by H-bonds (3). Hence, cocrystals represent multicomponent complexes where the Charge Transfer (CT) or Electron Donor-Acceptor (EDA) Interactions between two different molecules may determine the crystal packing that influences the solid-state properties of the cocrystal itself, and consequently the biopharmaceutical profile of the API included in the pharmaceutical cocrystals (4).

For the purpose of this initial screening of cocrystallization of the methylxanthine derivatives caffeine and pentoxifylline, three different types of Cocrystal Formers (or coformers, CF) [acetylsalicylic acid (ASA), alpha-Lipoic acid (ALA) and *p*-Coumaric acid (PCA)] have been selected on the base of their very common use in therapy in association with caffeine and pentoxifylline, respectively, as well as of the matching of proton acceptor/donor groups for each methylxanthine derivative with each of the three selected CFs.

Observation of the cocrystallized samples done by using Microscopy, and gained Raman and FT-IR Spectra indicate the formation of a new solid crystalline phase that is different from the solid phases of the starting substances prior the cocrystallization procedure. In addition, assignation of Raman and FT-IR spectra of the pure starting substances and their cocrystalized samples imply formation of cocrystals. Further characterization of solid crystalline phases by using Single Crystal Diffractiometry is expected to solve their crystal structures and to confirm the cocrystal formation.

(1) Dhaliwal, G.; Mukherjee, D. *Int. J. Angiol*. **2007**, *16(2)*, 36–44.
(2) Gresele, P.; Momi, S.; Falcinelli, E. *Br. J. Clin. Pharmacol*. **2011,***72 (4)* , 634–646.
(3) Dunitz, J. D. *CrystEngComm* **2003**, *5*, 506
(4) Bertolasi, V.; Gilli, P.; Gilli, G., *Cryst. Growth Des.* **2012**, *12*, 4758−4770