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

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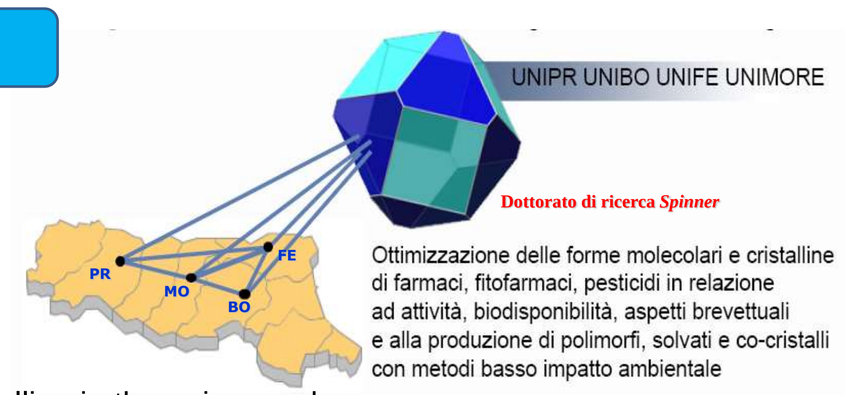
Introduction

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).



Objective

For the purpose of this initial screening of cocrystallization of the methylxanthine derivatives caffeine and pentoxifylline, and two different types of Cocrystal Formers (or coformers, CF) [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.

The purpose of this study is for first time explore an opportunities for formulation drug-drug type of Cocrystals for dual pharmacological response in therapy.

Methods

Microdroplet deposition technology (Microdrop Technologies GmbH, Germany) was applied in process of cocrystallization for binary system of CAF/ pCA. The solution CAF and pCA was prepared by dissolving pure starting substances in 1 : 1 stoichiometric ration into the 50/50 *w/w%* water-ethanol mixture and its application on the surface of the solid glass ribbons. Homogeneous deposited crystalline films that coated glass ribbons were noticed after their overnight drying on ambient temperature.

Binary solid systems PEN/ ALA were prepared by performing following methods:

-"Slow solvent evaporation" procedure for recrystallization of ethanol solution of dissolved PEN and ASA in1 : 1 stoichiometric ration;

- Grinding the powder of the starting substances was carried out manually in mortar with pistil in duration of 15 min.

- "Liquid Assisted Grinding" was performed by adding the few droplets of ethanol to powder mixture of PEN and ALA, kneading the paste mass during 15 min and its overnight drying on ambient temperature.

For preliminary characterization of the recrystallized binary solid systems CAF/pCA, Raman spectra were recorded on a Renishaw Ramascope (system 1000 with WireTM v1.3 Raman software) equipped with a Leica DMLM microscope and connected to a CCD charge-coupled device camera detector. The spectrometer was always calibrated against a Si-standard (520.0 cm−1) before starting the Raman measurements. A resolution of 4 cm-1 was used and 1,000 scans were recorded for each spectrum.

Samples of PEN/ ASA binary solids were characterized by recording FT-IR spectra on FT-IR Perkin-Elmer System 2000 spectrometer in 4000-400 cm-1 region, at room temperature.

References

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Gresele, P.; Momi, S.; Falcinelli, E. *Br. J. Clin. Pharmacol.* **2011,***72 (4)*, 634–646.

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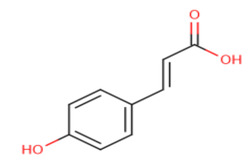
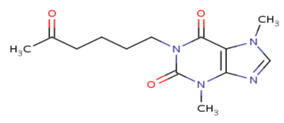
Data

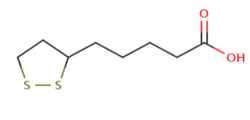
Caffeine (CAF)



p-Coumaric Acid (pCA)



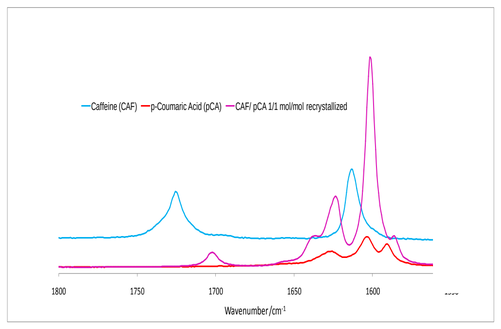
Pentoxyphylline (PEN)

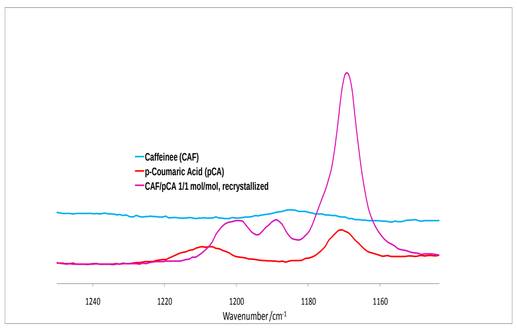


Alpha Lipoic Acid (ALA)

Results and Discussion

Cocrystallized binary systems with caffeine

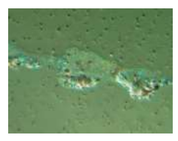




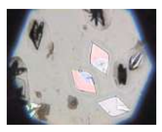
Experimental Raman wavenumber values

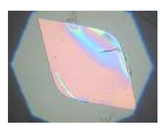
	cm^{-1}	Bands Assignments
Caffeine (CAF)	1185	
	1613	Carbonyl C=O stretching band
	1725	
***p*-Coumaric Acid (pCA)**	1171	
	1208	stretching and bending vibrations of the OH groups, short O—H…O hydrogen bonds
	1591	asymmetric stretching of the carboxylate moiety, *vas* (COO)
	1605	C=Casym stretching vibrations in the styrene moiety
	1630	C=C stretching frequency vas(C=C)sty; vas(C=O)
Binary Solid System CAF/pCA 1/1 mol/mol	1169	
	1189	
	1200	stretching and bending vibrations of the OH groups, short O—H…O hydrogen bonds
	1587	
	1601	asymmetric stretching of the carboxylate moiety, *vas*(COO)
	1624	C=Nasym stretching vibrations
	1638	
	1703	Completely dimerized carboxyl group with two hydrogen bonds to one neighboring molecule

Caffeine, pure



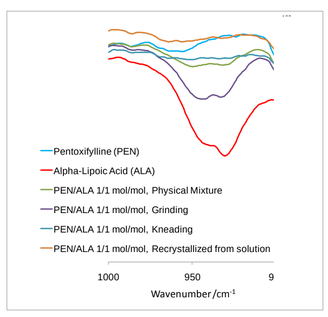
pCA, pure

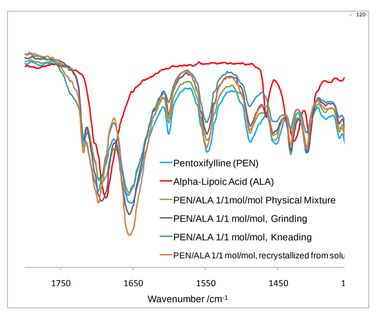


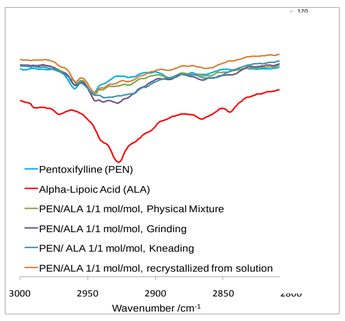


Cocrystallized new solid crystalline phase from CAF / pCA (1 : 1) mol/ mol binary solid system recrystallized from solution

Cocrystallized binary systems with pentoxifylline







Experimental FT-IR Spectra wavenumber values

	cm^{-1}	Bands Assignments
Pentoxifylline (PEN)	761, 752	– (CH2)n – skeletal vibration
	1656, 1422	–CH3 deformation mode
	1658	Amide –C=O stretching mode
	1720, 1701	C=O stretching mode
	2959, 2945	–CH stretching mode

	cm^{-1}	Bands Assignments
Alpha-Lipoic Acid (ALA)	932	Out of plane O—H bend of the carboxylic acid dimer
	1407	Symmetric carboxylate stretching mode
	1463	CH_2 scissoring band
	1600	absent
	1692	Completely dimerized –COOH with two hydrogen molecules to the neighboring molecule
	2930	C—H stretching bands

	cm^{-1}	Bands Assignments
Binary Solid System PEN/ALA 1/1 mol/mol Recrystallizeds from solution	1699, 1658	Amide –C=O stretching mode
	2962, 2947	–CH stretching mode

Conclusions

Recorded Raman spectra and observed new crystalline phase, distinct from starting substances, anticipate that solid crystalline binary system CAF/ pCA is cocrystal of caffeine and *p*-coumaric acid in 1/1 molar ration.

Further Work

Entire structural analyses based single-crystal diffractomery will elucidate the cocrystal composition and H-bonding motifs which link the molecule in cocrystal structure.

La XII Giornata della Chimica dell'Emilia Romagna, Ferrara il 17 Dicembre 2012