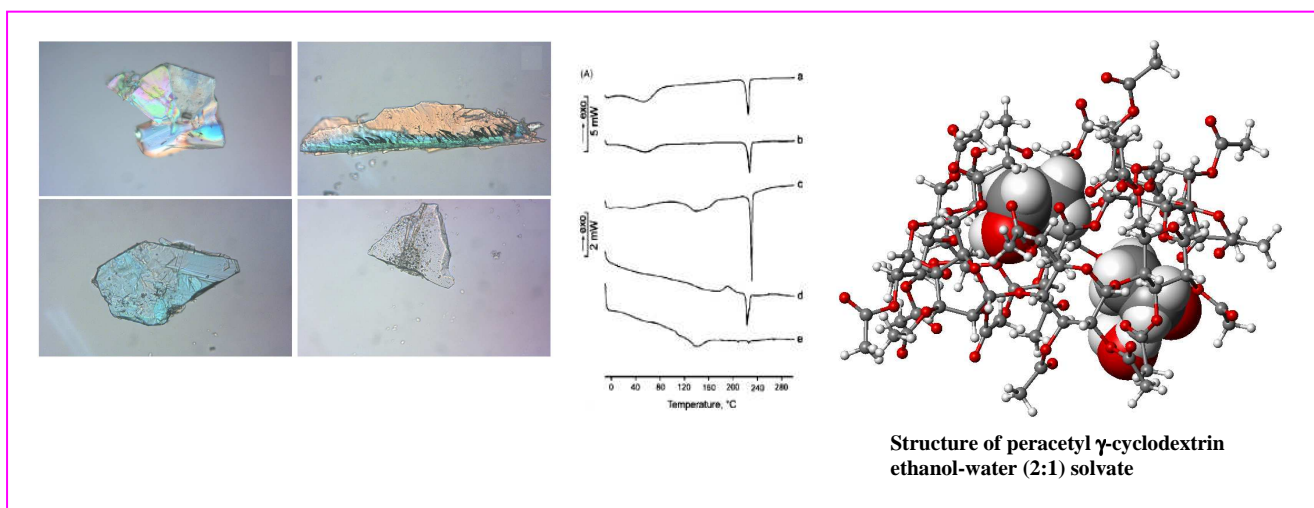


## Solid-state characterization of drugs, pharmaceutical additives, and their combinations

Prof. Giampiero Bettinetti – University of Pavia – Consorzio TEFARCO Innova

Giampiero Bettinetti's Group has substantial experience in the preformulation studies on solid drugs, i.e., physical chemical characterization of drugs, pharmaceutical excipients/additives, and their combinations. The research topic of special interest can be entitled "Thermal and structural characterization of pharmaceuticals: solid-state chemistry, polymorphism, pseudopolymorphism, amorphism, isostructurality, cocrystals, inclusion complexes, interaction products".

The current research deals with the characterization of peracetylated  $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclodextrins to be used as hydrophobic carriers for site-specific, prolonged release of vancomycin or teicoplanin in clinical situations such as prosthetic infections or bone infections.



### 1. Description of the product

Peracetyl  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin, and  $\gamma$ -cyclodextrin samples were prepared by recrystallization from various solvents, as well as by processing each cyclodextrin under the experimental conditions of kneading, evaporative crystallization, microwave irradiation and spray-drying used for preparing their interaction products with vancomycin or teicoplanin.

A number of crystalline forms of peracetyl  $\alpha$ -cyclodextrin (anhydrous and dihydrate), peracetyl  $\beta$ -cyclodextrin (two monotropic anhydrous polymorphs and three pseudopolymorphs) and peracetyl  $\gamma$ -cyclodextrin (two monotropic anhydrous polymorphs and two pseudopolymorphs, i.e. a hydrate isostructural with an isopropanolate-hydrate) as well as the amorphous forms of each peracetylcyclodextrin, were isolated and characterized. The first single-crystal X-ray structures of peracetyl  $\alpha$ -cyclodextrin were determined, and unique feature of the host molecule of partitioning its macrocyclic cavity (by self-inclusion of acetyl residues) into distinct sub-cavities that are filled with solvent molecules was demonstrated.

### 2. Innovative aspect of the product

Isostructurality of pharmaceutical solvates for various drugs, excipients, and co-crystals was investigated and fully characterized from the thermal and structural point of view. This phenomenon deserves attention from the viewpoint of drug formulation because a thermally very stable solvate can transform into the hydrate in the solid phase upon exposure to ambient air at ambient temperature, i.e., without direct contact with the liquid phase. Apart from the technological aspects, a hydrate presents less favourable

bioavailability characteristics (dissolution rate in water) than a solvate containing a solvent that is miscible with water.

### 3. Main advantages of the offer

Solid form diversity of pharmaceutical substances may influence the efficacy and safety of drug products. Physical chemical characterization of different solid phases that may occur during crystallization and pharmaceutical formulation processes is therefore advisable for both drugs and excipients.

In case of hydrophilic cyclodextrins, the amorphous or crystalline nature affects their technological properties as pharmaceutical excipients for tablets, as well as their solid-state interactions with hydrophobic drugs, which in turn influence the dissolution rate and drug stability. On the other hand, hydrophobic cyclodextrin derivatives such as peracetylated  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin, and  $\gamma$ -cyclodextrin can be used as bioabsorbable sustained-release carriers for hydrophilic drugs. Moreover, the crystalline nature of these carriers permits to investigate their solid-state interactions by thermal methods also with amorphous drugs.

### 4. Technology key words

Thermal analysis; Single-crystal and powder X-ray diffractometry; Infrared spectroscopy; Phase diagrams; Intrinsic dissolution rate; Cyclodextrin; Vancomycin; Teicoplanin.

### 5. Current Stage of Development

Development phase – laboratory tested.

### 6. Intellectual Property Rights

The product is not covered by patent

## Technical and scientific publications

G.P. Bettinetti, M. Sorrenti, L. Catenacci, F. Ferrari, S. Rossi, I. Salvadeo, P. Carraro. Solid-state interactions and drug release of teicoplanin in binary combinations with peracetylated  $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclodextrins. *J Incl Phenom Macroc Chem*, 57 (2007) 329–332.

M.R. Caira, G.P. Bettinetti, M. Sorrenti, L. Catenacci, D. Cruickshank, K. Davies. Effect of peracetylation on the conformation of gamma-cyclodextrin. *Chem Comm (Cambridge, England)* 28 (2007) 1221–1223.

M.R. Caira, G.P. Bettinetti, M. Sorrenti, L. Catenacci. Relationships between structural and thermal properties of anhydrous and solvated crystalline forms of brodimoprim. *J Pharm Sci* 96 (2007) 996–1007.

G.P. Bettinetti, M. R. Caira, M. Sorrenti, L. Catenacci, M. Ghirardi, L. Fábíán. Thermal studies of solvent exchange in isostructural solvates of a tetroxoprim-sulfametrole complex. *J Therm Anal Calorim* 77 (2004) 695–708.

M.R. Caira, G.P. Bettinetti, M. Sorrenti, L. Catenacci. Order-disorder enantiotropy, monotropy, and isostructurality in a tetroxoprim-sulfametrole 1:1 molecular complex: crystallographic and thermal studies. *J Pharm Sci* 92 (2003) 2164–2176.

## CONTACT

info@biopharmanet.eu

Tel.: +39 0521 905073 Fax: +39 0521 905006