title: Molecular mobility, phase transformations and stability of pharmaceutical materials under nanoconfinement

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Abstract

The main objective of the project is to explore and rationalize the influence of nanoconfinement on the dynamics, phase transformations and stability of pharmaceutics mainly by dielectric relaxation spectroscopy (DRS) in combination with temperature modulated calorimetry (TM-DSC) (to be purchased).

It is already established that amorphous and metastable forms of pharmaceuticals have improved bioavailability [1].Since they are unstable a major problem arises: how to produce and stabilize these forms as required for controllable drug delivery. Recently nano-confinement emerged as an approach to increase the lifetime of these more disordered states [2,3].Therefore, the guest confinement to nanopores is the strategy adopted in the present proposal, taking advantage of the know how of team and consultant (A Smirnov) in the synthesis and characterization of mesoporous (task 1). Since the improved bioavailability of the unstable drug forms is strictly connected with an enhanced molecular mobility relatively to the ordered crystal, our goal is motivated by the need of an understanding of the guest's dynamical behavior. To assess in situ, the molecular mobility of entrapped drug and guest-host interaction, DRS was chosen (task 2), representing a pioneer DRS application in the framework of pharmaceutical research devoted to the development of new drug delivery systems [4].The broad dynamical range covered by DRS allows probing a variety of motional length scales not accessible otherwise, in particular when the drug undergoes glass transition [5] similarly to conventional glass formers for which team and consultant (A Schoenhals) have already a

solid knowledge, bulk [6,7,8] and confined [9]. Recently motional modes of ibuprofen drug in both supercooled and glassy states were dielectrically characterized by some of us [10]. Following a specific thermal treatment a metastable crystalline phase was found the first time for ibuprofen, in a study leaded by the PI [11]. In spite of DRS probing also phase transformations as crystallization, the thermodynamical information to establish phase diagrams is only achieved by calorimetry (task 3) that has the advantage of being sensitive only to the confined guest (DRS senses also the host); the modulated method will also allow to distinguish real glass transition when cooperative multiple processes are detected by DRS. Complementary structural information of polymorphs will be performed by powder X-Ray (task 4). An additional problem is the compatibility with the hard pore which can be overcome by coating the pore wall with lipids [12] (task 5) that reflects also in drug delivery profile (task 6).

It is expected establish a correlation between different thermal pathways and phase transitions underwent by guests and to provide a detailed characterization of molecular dynamical events that persist in the state retained by the confined material that could enable further transformations

A broad scientific program will be undertaken bringing together a high level board with experts in -physical characterization and manipulation of condensed states -DRS -synthesis and characterization of mesoporous -peptides/proteins handling -evaluation of drug release Different teams from FCT/UNL, France-LDSMM, Germany-BAM, and USA-NCSU, are committed to achieve the project objectives
Moreover, the proposal will allow a multidisciplinary training in mesoporous production and general characterization techniques (FTIR, HPLC, UV-Vis), dielectric relaxation spectroscopy, differential scanning calorimetry, X-ray, being expectable that hired fellowships continue as PhD students.

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