A Strategy for Determining the Atomic-Resolution Structure of Micro-/Nanocrystalline Composite Solids

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For over 60 years, nanomaterials have consistently attracted the attention of the scientific community. In the field of nanomedicine, recent effort toward optimizing the therapeutic efficacy of newly discovered active compounds has resulted in the development of original supramolecular systems that execute multiple functions. However, the true potential of these systems has not been entirely utilized. Advancing these materials calls for precise structural analysis of individual elements and a description of the mutual relations between them. This is a stringent requirement, as these systems exist at the borderline between crystalline and amorphous solids, for which high-quality diffraction data are inherently unavailable. This contribution thus addresses our attempt to formulate an efficient experimental-computational strategy for obtaining deep insight into the structure of complex polycrystalline composites with micro- and nanodomain architecture. To determine the atomic-resolution structure of these systems, we apply a procedure based on ^{1}H NMR crystallography extended to describe the component-selective data. This strategy is based on the combined application of domain-selective solid-state NMR spectroscopy (ss-NMR), crystal structure prediction (CSP), and density functional theory (DFT)-based calculations of NMR chemical shifts. This combination of experimental and theoretical approaches enables one to determine the structural arrangements of molecules in situations which are not tractable by conventional spectroscopic techniques. Its applications should be of particular importance for systems in which phase transformations can occur, and new polymorphic forms can be spontaneously created under the influence of the matrix environment. The potential of this combined analytical approach is highlighted using the recently developed biodegradable, injectable polyanhydride microbead formulation of decitabine (5-aza-2'-deoxycytidine, DAC), an archetypal DNA methyltransferase inhibitor used as an efficient therapeutic for epigenetic cancer therapy. In this innovative drug-delivery formulation, which was developed to circumvent the problem of hydrolytic lability of the active compound, a mixture of microcrystalline domains of decitabine and nanodomains of sebacic acid (SA) is embedded in the semicrystalline matrix of poly(sebacic acid-co-1,4-cyclohexane-dicarboxylic acid) (PSA-co-PCH) carrier. The proposed method, which employs the confluence of computational data with measured NMR parameters, thus provides for a way to distinguish between alternative candidate structures exclusively existing in the composite assembles, and to select the ones that are the most compatible with available information. As the obtained results also opened a route toward the structure refinement of synthetic polymers with a limited amount of spectroscopic data available, finding a procedure for the reliable generation of a representative set of CSPs of synthetic polymers is thus of paramount importance. This contribution thus demonstrates the synergy effects of the proposed combination of several experimental and computational procedures, which considerably extends the NMR crystallography approach into the area of intricate mixtures and nanostructured composites. Potentiality of this approach will be also highlighted in de-nuovo determination of the crystal structure of chemotactic N-formyl-L-Met-L-Leu-L-Phe-OH tripeptide.

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