Hybrid Biomaterials: Atomic-Level Insights into Structure, Dynamics, and Functionality for Nanobiomedicine

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Introduction

Many newly discovered drugs never reach their therapeutic potential due to unfavorable physicochemical properties such as poor solubility, low stability, or inadequate bioavailability. To address these limitations, multi-component drug-delivery solids have emerged as versatile platforms capable of combining multiple functions within a single material. These systems often feature hybrid architectures comprising crystalline, amorphous, and semicrystalline domains, as well as interfaces between organic and inorganic components. Their biomedical utility strongly depends on precise structural organization, which determines stability, release behavior, and biological interactions.

However, unraveling the atomic-level structure of such complex systems remains a major challenge. Conventional diffraction techniques often fail to provide sufficient insight, particularly for heterogeneous, partially ordered, or multiphase materials. In this work, we present an integrated strategy based on solid-state NMR crystallography, advanced quantum-chemical modeling, and statistical data analysis to obtain atomic-resolution structural information on multicomponent drug-delivery systems. This methodology is demonstrated on three representative examples: (i) injectable polyanhydride microbeads with decitabine [1], (ii) silica-based liquisolid systems loaded with tapentadol [2], and (iii) alginate–pectin hybrid microparticles encapsulating self-emulsifying systems (SES) [3,4].

Experimental

Our approach relies on the synergistic combination of experiments and computations:

- **Solid-state NMR spectroscopy**: including ^{1}H MAS, ^{13}C MAS and CP/MAS, and 2D ^{1}H–^{1}H MAS NMR, which provide local structural and dynamic information independent of long-range order.
- **Complementary techniques**: FTIR and X-ray powder diffraction (XRPD) were employed to validate global crystallinity and identify partially ordered regions.
- **Quantum-chemical calculations (DFT)**: optimized molecular geometries and predicted NMR parameters, enabling direct comparison with experimental values.
- **Statistical analysis**: large datasets were analyzed using multidimensional factor analysis to discriminate overlapping spectral contributions and assign them to specific domains or interactions.

This workflow allows us to disentangle complex multiphase systems, map their nanoscale architecture, and relate atomic-level structure to functional properties.

Results and Discussion

Injectable polyanhydride microbeads: The first case concerns poly(sebacic acid)-based injectable microbeads incorporating microcrystalline decitabine and nanocrystalline sebacic acid. Solid-state NMR spectra, supported by DFT parameter predictions, revealed the coexistence of distinct crystalline populations embedded in a semicrystalline polymer matrix. Through-space dipolar couplings confirmed nanoscale domain segregation. This dual-domain architecture explains the simultaneous stability of the carrier and controlled release of the active compound, essential for injectable formulations.

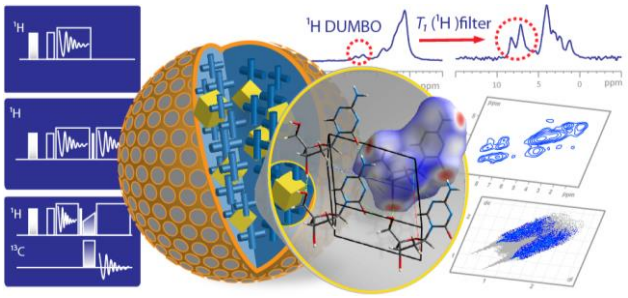

Figure 1. Injectable polyanhydride microbeads

Liquisolid silica systems with tapentadol: In the second case, we investigated mesoporous silica carriers loaded with tapentadol in glucofurol solvent. Surprisingly, straightforward solid-state NMR measurements unveiled a previously unknown low-molecular-weight organogel phase confined within silica pores. 2D ^{1}H–^{1}H MAS NMR and quantum-chemical modeling showed that tapentadol molecules self-assemble into hydrophobic aggregates stabilized by –OH…π interactions and π–π stacking, which suppress hydrogen bonding with the solvent. This discovery highlights the ability of confined environments to induce unique, non-bulk molecular organizations that cannot be detected by conventional methods. The structural understanding also provides direct design principles for tuning drug release kinetics and stability in mesoporous carriers.

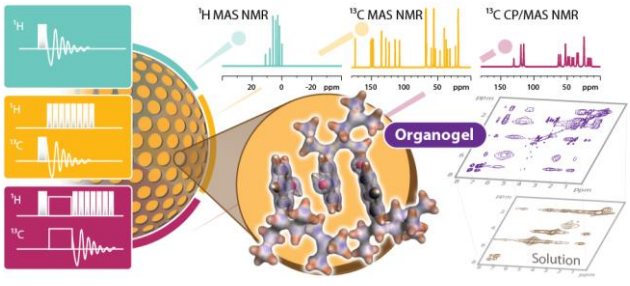

Figure 2. Liquisolid silica systems with tapentadol

Hybrid alginate–pectin microparticles with SES: The third case addresses alginate–pectin co-networks dually crosslinked by Ca^{2+} and Zn^{2+} ions, encapsulating self-emulsifying systems for delivery of lipophilic phytotherapeutics. Alginate and pectin are widely applied polysaccharides due to their biocompatibility, mucoadhesion, and tunable crosslinking. Nevertheless, the molecular details of their hybrid interactions have been elusive. Our integrated analysis revealed the coexistence of two alginate chain types: rigid chains stabilized by strong interactions with pectin, and more flexible chains located in domains beyond pectin's influence. SES droplets were evenly dispersed within the network, interacting at well-defined interfaces with methoxylated pectin aggregates. These interactions increased crosslink density, restricted segmental dynamics, and reinforced network integrity. The result is a material with enhanced stability, controlled release properties, and improved mucoadhesion, making it particularly attractive for long-term site-specific therapies such as intestinal inflammation treatment.

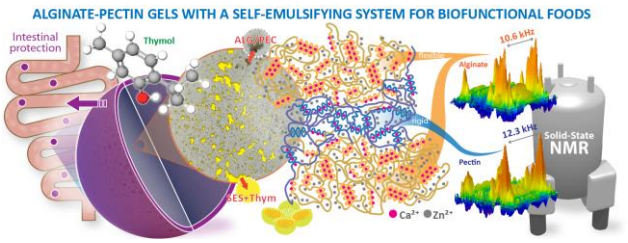

Figure 3. Hybrid alginate–pectin microparticles with SES.

Conclusion

The presented work demonstrates how a combined NMR crystallography–computational–statistical strategy enables unprecedented insight into multicomponent biomaterials at atomic resolution. Across three distinct systems—polymeric microbeads, silica-based liquisolid carriers, and hybrid polysaccharide gels—we show how local molecular packing, nanoscale domain segregation, and interfacial interactions govern key functional properties such as stability, release behavior, and bioavailability.

By identifying previously unknown structural phases, such as the confined organogel of tapentadol and dual alginate chain populations, this approach highlights the importance of atomic-level characterization for the rational design of next-generation nanobiomaterials. Beyond the specific systems studied, the methodology is broadly applicable to complex drug-delivery solids, offering a general framework to link structure, dynamics, and function in biomedical materials.

Acknowledgments

This research was supported by the project New Technologies for Translational Research in Pharmaceutical Sciences / NETPHARM (CZ.02.01.01/00/22_008/0004607), co-funded by the European Union.

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