1. Title of Case Study: NMR Studies of Soft Matter

2. Grant Reference Number: EP/P019943/1, EP/N033337/1, BB/X011054/1

3. One sentence summary: ^{1}H, ^{13}C and ^{19}F NMR spectra obtained at the UK High-Field Solid-State NMR National Research Facility provide structural and dynamic insight into the organisation of soft-matter systems where domains with different ordering and dynamic states coexist in complex multiphase assemblies such as hydrogels, liposomes and plant-based biomaterials.

4. One paragraph summary:

NMR spectroscopy is a powerful analytical tool for characterising the structure of molecules and materials with atomic resolution via the local magnetic interactions that are sensitive to the local electronic environment of the atomic nucleus as well as dipolar and J couplings of nuclear spins that inform on through-space proximities and through-bond connectivities. For soft matter systems, the usual challenges of solid-state NMR spectroscopy related to the need of averaging out anisotropic magnetic interactions via magic-angle spinning (MAS) are amplified by the technical demands of using MAS on multiphasic materials and the very much reduced sensitivity due to very high content of a solvent or other phase-forming species (e.g., lipids in liposomes). This case study describes the application of combined solid- and solution-state advanced NMR tools to characterise different aspects of the structure, dynamics and interfacial connectivities in soft matter systems, benefitting from the enhanced resolution and sensitivity provided by working at the high magnetic fields of the UK High-Field MHz Solid-State NMR National Research Facility (NRF). By combining NMR findings with the data from other advanced characterisation tools that probe structure and dynamics in these systems at different length and time scales, a generic tool-kit of methods for assessing the structure and interface interactions in very challenging soft matter systems has been developed. Such fine detail in structural analysis is of importance for the development of soft matter systems for applications in different fields encompassing pharmaceuticals, biomaterials, food and home-care industries.

5. Key outputs in bullet points:

- *A generic tool-kit of solid- and solution-state NMR methods for assessing molecular-level organisation and interface connectivities suitable for studies of different classes of soft matter systems.*
- *Molecular-level understanding of key interfacial interactions that govern the formation of metastable soft-matter materials; this insight is critical information for directing industrially relevant applications of such materials in different fields.*
- *Use of NMR crystallography (comparison of experiment to NMR chemical shifts and quadrupolar parameters calculated using density-functional theory) in combination with solution-state NMR to quantify the effect of specific key intermolecular interactions on the self-assembly of molecular soft-matter systems.*

6. Main body text

NMR characterisation of soft matter systems relies on the combined application of advanced solid- and solution-state NMR focussing on the rigid and mobile constituents, respectively, in these complex heterogeneous structures. NMR characterisation has been performed at a magnetic field strength of 20 Tesla (corresponding to a ^{1}H Larmor frequency of 850 MHz) in projects of relevance to Unilever, Croda and Iceni Diagnostics.

^{19}F NMR provided the benefit of enhanced sensitivity of particular importance for detecting gelators or guest molecules that are distributed between different compartments of soft-matter systems.

Williamson et al. have developed a ^{19}F solid-state MAS NMR methodology to determine the partitioning of these (non-UV-active) compounds into lipid vesicles without the need for separation of the vesicles. The method utilizes ^{19}F MAS NMR to quantitatively characterise the partitioning of the fluorinated compounds between the aqueous and membrane phases. Khimyak et al. used combined solid- and solution-state NMR ^{13}C, ^{19}F, ^{13}C-^{19}F and ^{1}H based methods to identify enzymatically produced nanofibers due to a new allomorph of cellulose and to assess the effect of introducing of ^{19}F labels on the local ordering, both in the bulk and at the surfaces of such assemblies.
A similar combination of ^{13}C and ^{1}H solution- and solid-state NMR methods enabled Khimyak et al. to characterize the structure of bacterial cellulose (BC) ribbons at ultra-high resolution and to monitor the local mobility and water interactions in the hydrogels obtained in the presence of the "guest" glucans, thus identifying their effect on the short-range order, mobility, and hydration of BC fibres.
Warren and Khimyak et al. employed a range of NMR methodologies enabling simultaneous detection of mobile and rigid components and water/carbohydrate interactions to probe the molecular mobility and water dynamics in starch hydrogels featuring a wide range of physical properties. The presence of highly dynamic starch chains, behaving as solvated moieties existing in the liquid component of hydrogel systems was correlated to their macroscopic and biochemical properties, thus facilitating the tailored study and design of novel, environmentally friendly soft matter biomaterials for future use.
By employing a combined solution- and solid-state NMR approach for the study of the assembly of G-quadruplexes, Brown et al. identified the crucial role played by solvent effects and ion concentration on the structural integrity, and hence functionality of G-quadruplexes in the solid state as compared to in solution. Distinct N-H···N and N-H···O intermolecular hydrogen bonding interactions drive quartet and ribbon-like self-assembly resulting in markedly different 2D ^{1}H solid-state NMR spectra, thus facilitating direct identification of mixed assemblies.

References:
Williamson et al, Angew. Chem. Int.Ed. 2023, 62, e202301077; DOI: doi.org/10.1002/anie.202301077
Khimyak et al, Chem. Eur. J. 2021, 27, 1374 –1382, 2021 DOI: 10.1002/chem.202003604
Khimyak et al, Biomacromolecules 2019, 20, 4180-4190 DOI: 10.1021/acs.biomac.9b01070
Khimyak, Warren et al, Carbohydrate Polym. 2020, 249, 116834 DOI: 10.1016/j.carbpol.2020.116834
Brown et al, Chem. Eur. J. 2017. 23, 2315-2322, DOI: 10.1002/chem.201604832

7. Names of key academics and any collaborators:

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9. Who should we contact for more information?

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