Probing nanocellulose surface chemistry at natural isotopic abundance: overcoming current characterization limitation with MAS-DNP

Akshay Kumar*[1], Hippolyte Durand[2], Elisa Zen[3], Cyril Balsollier[4], Bastien Watblet[3], Sébastien Fort[4], Isabelle Baussane[5], Daniel Lee[6], Naceur Belgacem[2], Sabine Hediger[1], Martine Demeunynck[5], Julien Bras[2], and Gaël De Paepe[1]

[1]Univ. Grenoble Alpes, CEA, CNRS, IRIG-MEM – Commissariat à l'Énergie Atomique et aux Énergies Alternatives (CEA) - Grenoble – Grenoble, France

[2]Univ. Grenoble Alpes, CNRS, Grenoble-INP, LGP2 – Univ.Grenoble Alpes, CNRS, Grenoble-INP, LGP2 – Grenoble, France

[3]Centre Technique du Papier (CTP) – Centre Technique du Papier – Grenoble, France

[4]Centre de Recherches sur les Macromolécules Végétales (CERMAV-CNRS – Centre de Recherches sur les Macromolécules Végétales – Grenoble, France

[5]Département de Pharmacochimie Moléculaire (DPM), UMR5063 CNRS/UGA – Département de Pharmacochimie Moléculaire, CNRS : UMR5063, Université Grenoble Alpes St Martin d'Hères, – Grenoble, France

[6]Department of Chemical Engineering Analytical Science (CEAS), Univ of Manchester – Manchester, Royaume-Uni

Résumé

In addition to being renewable, biodegradable, and biocompatible, cellulose nanofibrils (CNF) possess a high specific area, which makes them an ideal candidate as carriers in drug delivery applications. Prodrugs with tailored linkers providing stimuli-responsive on-demand drug release ability can be covalently grafted on CNF using green chemistry routes. However, the in-depth chemical and structural characterization of the CNF surface chemistry is often an unmet challenge that goes beyond the current sensitivity and resolution limits of standard characterization techniques, especially for low weight percentage ($< 5\%$) of functionalization (Johan et al ., Chem. Soc. Rev., 2018). Nevertheless, accurate information on low-level CNF surface modifications is mandatory for the development of advanced surface chemistry routes for the design of nanocellulose based drug delivery carriers that ensure safety, dosing, and control of delivery kinetics.

Solid-State NMR (SSNMR) spectroscopy is, in principle, a key technique to obtain structural information on this type of systems. It has indeed been used in the past for studying nanocellulose surface chemistry, but at higher levels of grafting ($> 10\%$) and using isotopically labeled molecules. However, owing to its intrinsic low sensitivity for non-abundant isotopes like 13C, solid-state NMR fails to address low levels of grafting ($< 5\%$) at natural isotopic abundance. This is notably the case for the system studied here, a biologically active antibiotic drug carrier with on-demand drug release ability, composed of cellulose nanofibrils

*Intervenant

functionalized with anti-bacterial prodrug (metronidazole).
To overcome the sensitivity limitation of SSNMR and to investigate surface functionalization of this biologically active material, we used Magic Angle Spinning Dynamic Nuclear Polarization (MAS-DNP). We notably show that MAS-DNP is the only technique that can unambiguously probe the surface of this system. In only 2 hours of experimental time, we were able to provide answers to the three following major questions: the degree of functionalization (1% in our case), differentiating between bound and adsorbed chemical species, and the presence of unwanted by- and side - products in the final product. Moreover, we highlight the limits of conventional characterization techniques such as FT-IR, conductometric titration, elemental analysis and conventional SSNMR, which all failed to characterize this system, leading even to misleading conclusions (Akshay et al., Chem. Sci., 2020). The method demonstrated here can be extended to the surface characterization of other organic nano materials with low-level of grafting, and the optimization of their synthesis.