Solid and Solution NMR Characterisation of Modified Dextrans for Drug Delivery

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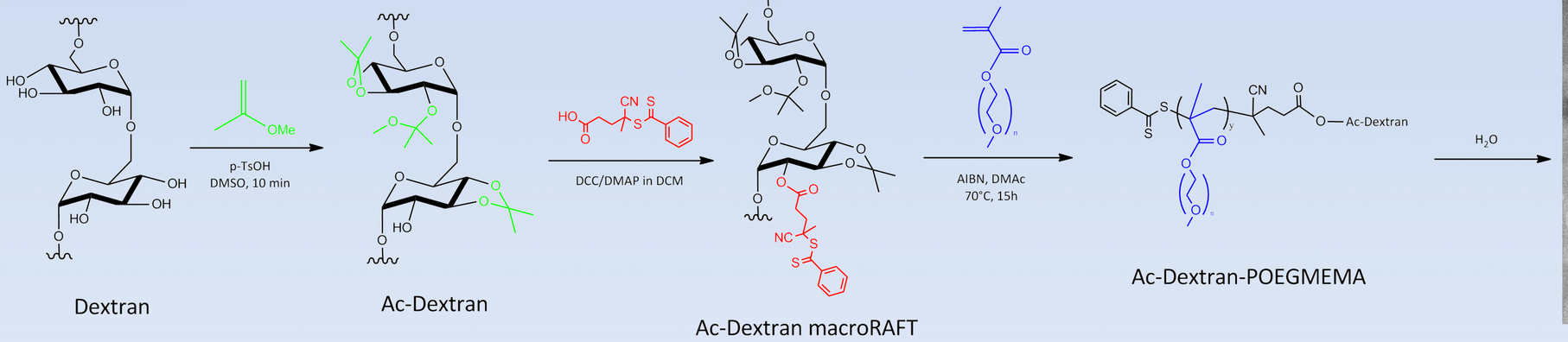
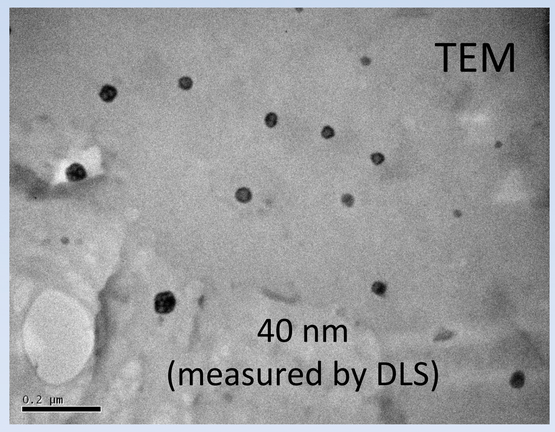
Background

The safe and effective delivery of drugs (eg. anticancer drugs) is a significant challenge for many reasons – drugs are often poorly soluble; harsh environments in the body can damage drugs before they reach the target area; drugs can be cleared by the body's defence mechanisms; and the lack of selectivity can cause reduced concentrations at the diseased sites and cause potentially severe side effects. Many of these problems can be overcome by the use of well-designed polymeric drug carriers. Desirable characteristics include the use of biodegradable polymers; stimuli-sensitive systems to release the drug preferentially at targeted sites; and nano-sized carriers to take advantage of passive targeting via the enhanced permeation and retention effect. This study aimed to make a biodegradable, pH-sensitive polymer based on dextran which would self-assemble into nanocapsules in water for the delivery of anticancer drugs eg. doxorubicin.

Synthesis

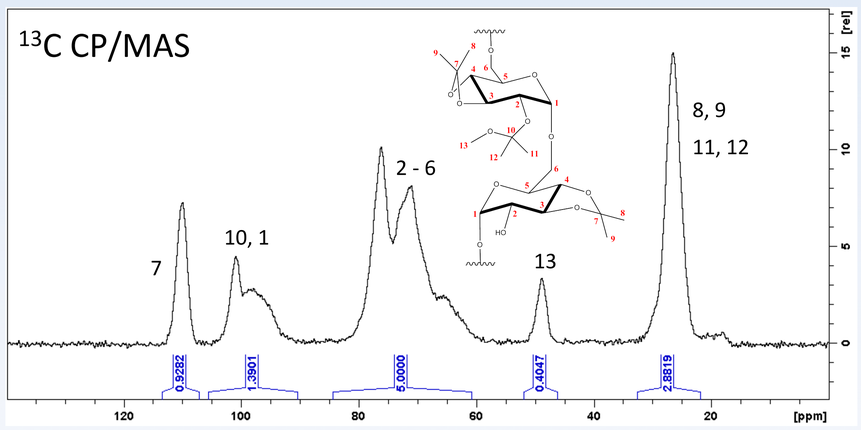


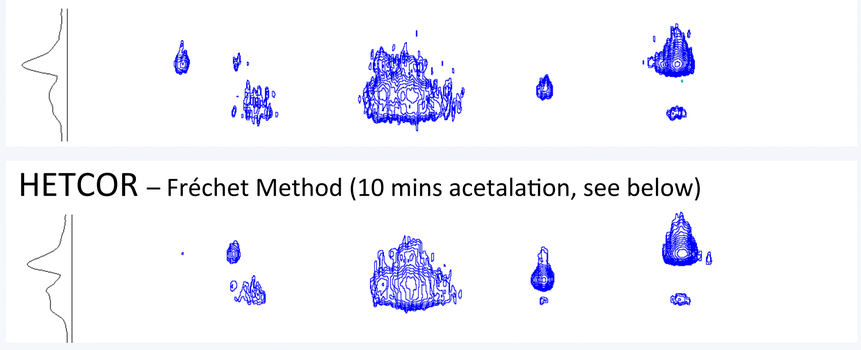
Dextran — Ac-Dextran — Ac-Dextran macroRAFT — Ac-Dextran-POEGMEMA



Acetalated Dextran

Solid state NMR





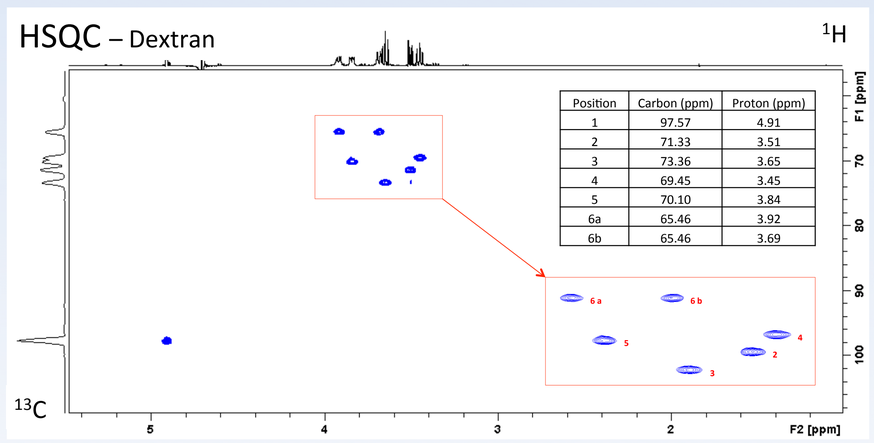
Acetalated dextran is a relatively new material for drug delivery, and so few methods exist to determine important characteristics.

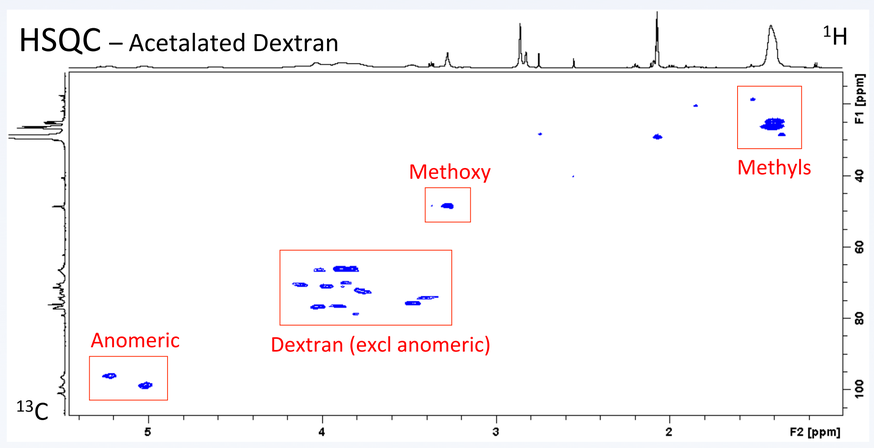
We have applied both solid state and solution NMR to determine the following:

- Degree of substitution (DS) – the number of substitutuents per 100 repeating units
- Ratio of acyclic to cyclic acetals
- % Hydroxyl coverage
- Number of acetals and free hydroxyls per chain (62 repeating units per 10,000 g mol^{-1} chain)
- Molecular weight
- Substitution patterns (?)

DS acyclic	40
DS cyclic	93
Ratio acyclic : cyclic	1 : 2.3
OH coverage	75%
No. acyclic per chain	25
No. cyclic per chain	58
No. free OH per chain	45
Molecular weight	14,100 g mol^{-1}

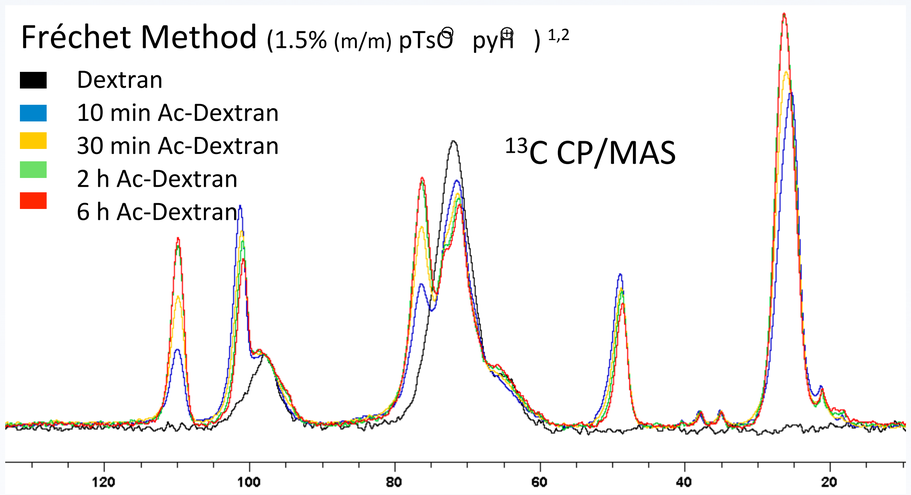
Solution NMR

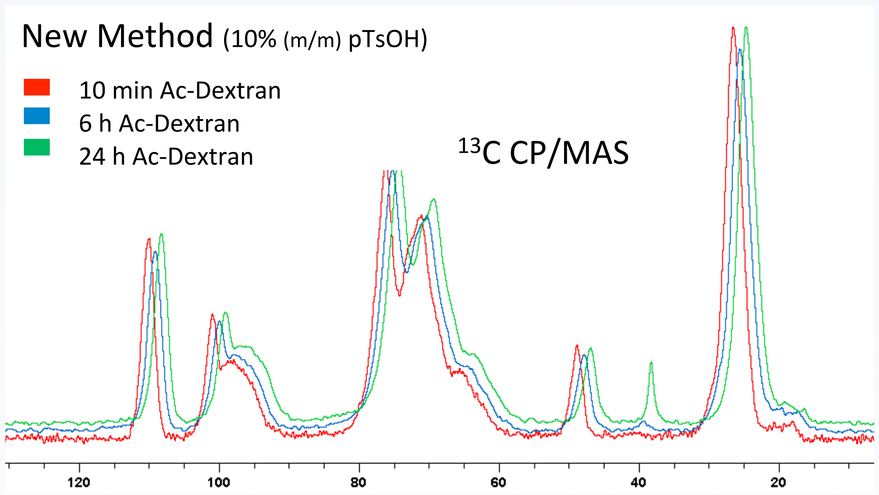




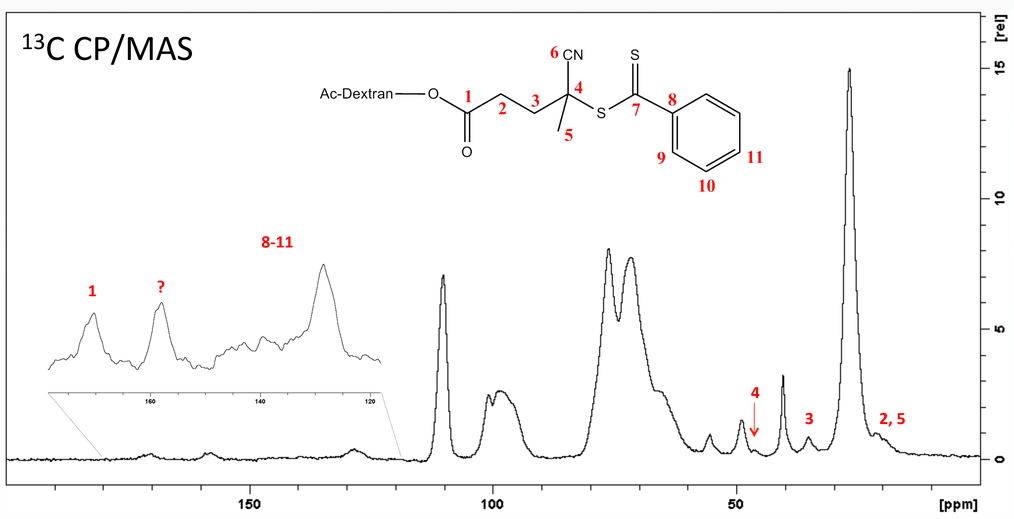
Acetalation Kinetics

The acetalation method was a modified version of the Fréchet method [1,2] using the catalysts shown. Solid state ^{13}C CP/MAS was particularly useful to investigate kinetics. This showed that the new catalyst was significantly more efficient at producing cyclic acetals, the desired product, and that the reaction went to completion in less than 10 minutes.

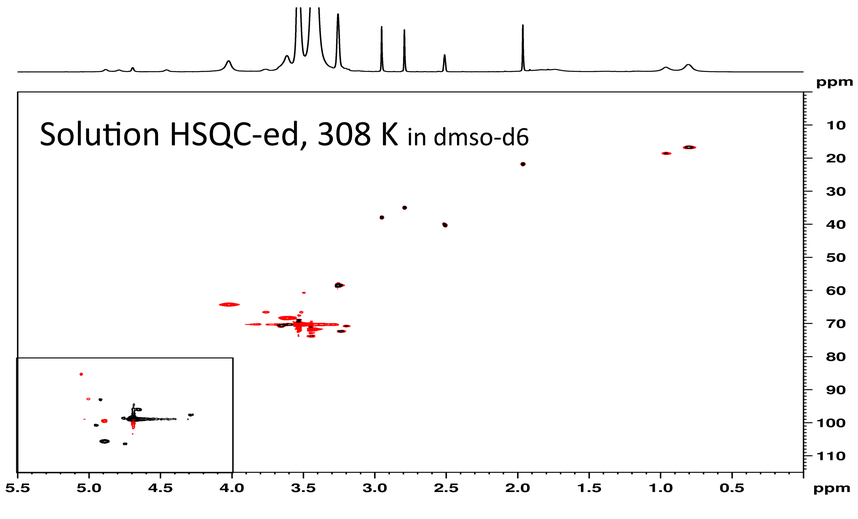




Ac-Dextran macroRAFT



Ac-Dextran-POEGMEMA



References: [1] E. M. Bachelder et al., *J. Am. Chem. Soc.* **2008**, *130,* 10494-10495; [2] K. E. Broaders et al., *J. Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 5497-5502