Nanogels of Hydrophobized Methylcellulose

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Statement of Purpose: Due to their convenience, eye drops account for approximately 90% of commercially available ophthalmic formulations. However, rapid pre-corneal loss drastically limits their efficiency. Between 1% and 5% of the drug reaches the intraocular tissues; the remainder of the drug dosage undergoes nonproductive systemic uptake which may result in serious adverse effects (Mudgil M. Int J Pharm Sci. 2012;4:105–112).

Hydrophilic nanogels are easily dispersed in aqueous media. Able to encapsulate bioactive compounds and release their payload in a controlled fashion, such formulation could improve the topical ocular therapy by reducing dosage and frequency of administration.

Polysaccharides partially modified with hydrophobic moieties have been shown to form nanogels through a self-assembly process in an aqueous environment (Akiyoshi K. Macromolecules. 1993;26:3062). In this study, nanogels were synthesized by grafting methylcellulose with hydrophobic chains of poly(N-tert-butylacrylamide).

Methods: Poly(N-tert butylacrylamide) (PNtBAm) side chains were grafted on a methylcellulose (MC) backbone via cerium ammonium nitrate (CAN). Synthesis was confirmed by ^{1}H nuclear magnetic resonance (NMR) and attenuated total reflectance (ATR), and grafting was quantified by elemental analysis. Nanogels where characterized with dynamic light scattering (DLS) and transmittance electron microscopy (TEM). Finally, release of dexamethasone from the nanogels was examined and quantified by high-performance liquid chromatography (HPLC).

Results: NMR confirmed successful grafting of PNtBAm onto methylcellulose showing the butyl groups peak at 1.26ppm (Figure 1).

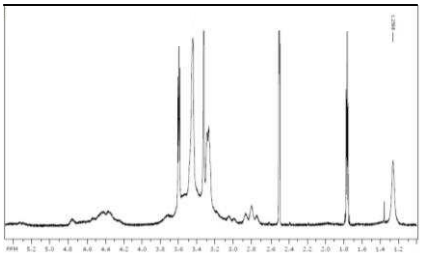

Figure 1. ^{1}H NMR spectra of MC-g-PNtBAm.

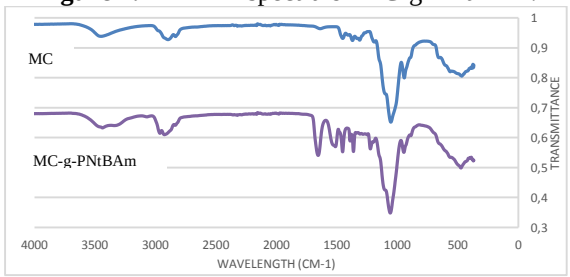

Figure 2. ATR spectra of MC and MC-g-NtBAm.

ATR (Figure 2) shows a peak at 1651cm^{-1} assigned to the characteristic adsorption of the carbonyl groups of the ring opening of the MC backbone. The absorbance band at 1510cm^{-1} is attributed to the secondary amine bending and the peaks at 1390/1361/1224cm^{-1} are associated with the butyl groups of PNtBAm.

Synthesized molecules (MC-g-PNtBAm) self-assembled in water driven by hydrophobic interaction of the grafted side chains. Materials were synthesized varying the degree of hydrophobic modification by changing initiator and monomer concentrations (Table 1) resulting into different assembling of the molecules.

Table 1. Composition of synthesized materials.

Material	F3L5	F3L30	F18L5	F18L30
Initiator ratio per MC chain	3	3	18	18
NtBAm ratio per MC chain	15	90	90	540

DLS was used to further study the size of the colloid and showed that increasing hydrophobic grafting induced an increase in the size of the assemblies, ranging from 107.8 nm to 1272 nm.

The morphology of the colloids was observed under TEM (Figure 3). Several assembling scales were revealed. The lowest hydrophobic modification, induced the formation of fewer loose particles, while the highest led to precipitate formation. F18L5 turned out to be the best composition for self-assembling into nanogels.

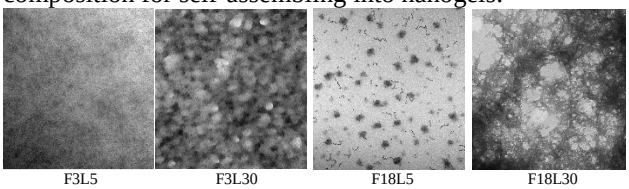

Figure 3. TEM pictures, magnification 75K.

F18L5 was thus tested for release of dexamethasone. It provided an entrapment of 94%, justified by its assembling into nanogels and the affinity of dexamethasone for the hydrophobic domains created by the PNtBAm chains. The initial burst corresponds to the drug not entrapped, followed by a slow release of the drug from the nanogels.

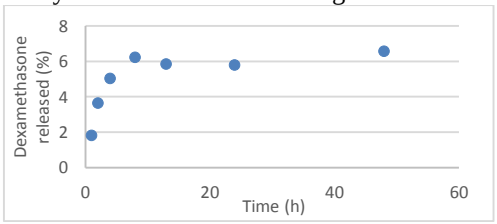

Figure 4. Dexamethasone release of F18L5 nanogels.

Conclusions: Nanogels made of MC grafted with PNtBAm were successfully synthesized via cerium ammonium nitrate. Nanogel formation showed to depend on CAN and NtBAm feed ratios. Nanogels showed efficient entrapment of dexamethasone and slow release profile over several days. Future work will aim at further optimizing the synthesis of the nanogel and characterizing these materials to progress their potential for entrapment and release of bioactive compounds.