**Non-toxic In Situ Gelable Hydrogels Formulated from Oxidized Dextran and *N*-Carboxyethyl Chitosan**

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**Introduction:** Hydrogel is a versatile class of material and its unique properties could be adapted and tailored to resemble the general properties of biological tissues. In situ rapid material gelation to form hydrogel is advantageous for many biomedical applications. However, many in situ gelable systems are either cumbersome to prepare or require potentially cytotoxic reagents. The objective of this study was to characterize a reagent-free, non-toxic in situ gelable hydrogel system formulated from oxidized dextran (Odex) and *N*-carboxyethyl chitosan (CEC).

**Methods: Synthesis of CEC and Odex:** CEC was synthesized according to a scheme reported previously [1]. Odex was prepared by first dissolving 5g of dextran in 400mL of ddwater, then adding $NaIO_4$ in 25% molar equivalent (in 100mL ddwater) under rapid stirring at ambient temperature for 24hrs. Diethylene glycol was added to quench the unreacted $NaIO_4$, and purified Odex was obtained after exhaustively dialyzed for 3 days followed by lyophilization (yield, 80%). The molecular weights of Odex were determined by HPLC (Waters 600e, USA) using 0.1M $KNO_3$ as a mobile phase at a flow rate of 0.8mL/min at ambient temperature. Dextran standards (Fluka Chemie AG, Switzerland) in the molecular range of 12–80 kDa were used for calibration. **Hydrogel Preparation**: Odex solutions were mixed with CEC solutions in a ratio of 5:5. The mixtures were gently stirred for 10s for homogenous mixing and kept at 25°C for 12h for gel formation. **Rheometry**: The rheology measurements were performed on a rheometer (Physica MCR 301, Anton Paar, UK). For time sweeping tests, the storage moduli G′ and loss moduli G″ were monitored as a function of time at a frequency 1 rad/s and a stress strain 2% at a constant temperature 37 °C. **Scanning electron microscopy (SEM) analyses:** A field-emission SEM (SFEG Leo 1550, AMO GmbH, Aachen, Germany) at 20 kV was used.

**Results/Discussion:** The time dependence of storage moduli (G′) and loss moduli (G″) for a 5:5 Odex/CEC (concentration: 1.5% for both) at 37°C was depicted in Figure 1. At $t < t_{gel}$, G′ was lower than G″, corresponding to an Odex/CEC sol. Both moduli elevated rapidly as gelation proceeded; the buildup rate of G′ was much higher than that of G″ due to the occurrence of crosslinking through Schiff base formation between aldehyde residues of Odex and amino residues of CEC. The crossover of G′ and G″, defined as the gel point ($t = t_{gel}$), indicative of transition of the Odex/CEC system from a liquid-phase to a solid-phase, suggesting formation of 3-D networks. The $t_{gel}$ deduced was 103s, implying rapid gelation of the Odex/CEC system. $\eta^*$ of the system also underwent a similar algorithm (i.e., rapid buildup in the beginning followed by a plateau).

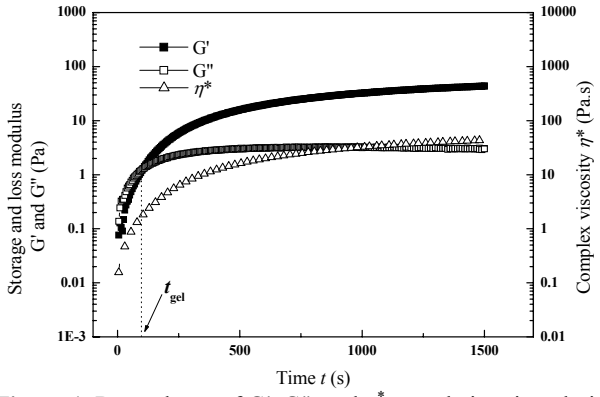


**Figure 1.** Dependence of G′, G″, and $\eta^*$ on gelation time during the gelation process for a 1.5% Odex/CEC mixed solution at 37°C. The gel point is denoted as $t_{gel}$.

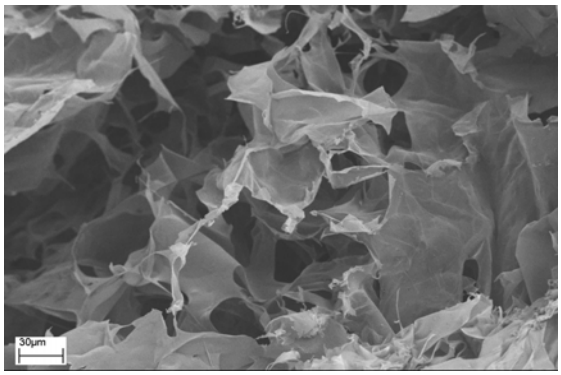


**Figure 2.** SEM image of the Odex/CEC hydrogel formulated from a 1.5% Odex/CEC mixed solution.

Figure 2 depicted the SEM image of a fractured lyophilized hydrogel formulated from a 1.5% Odex/CEC mixed solution. The hydrogel has a highly porous interior structure with an average pore size of 50μm, indicating its high water retention ability. Small or macromolecuar drugs could theoretically diffuse freely into the hydrogel. Furthermore, a very thin layer of material on the suface of the hydrogel partially covering the pores was observed.

**Conclusions:** A novel in situ crosslinkable hydrogel formulated from Odex and CEC was successfully prepared without the need of using any small molecular crosslinkers. The Odex/CEC system could gel within 2 min to form a highly porous hydrogel. The system has potential for many biomedical applications including filling aneurysm and arteriovenous malformation.

**References:**

[1] Jiang H, Wang Y, Huang Q, Li Y, Xu C, Zhu K, Chen W. Macromol. Biosci. 2005, 5, 1226–1233.

**Acknowledgment:** This study was funded by NIH (DK068401). The authors would also like to thank Mr. Christopher Judd (Engelhard, Inc.) for HPLC analyses; and Dr. Xuming Chen (Chemistry Department) for his assistance in rheological analyses.