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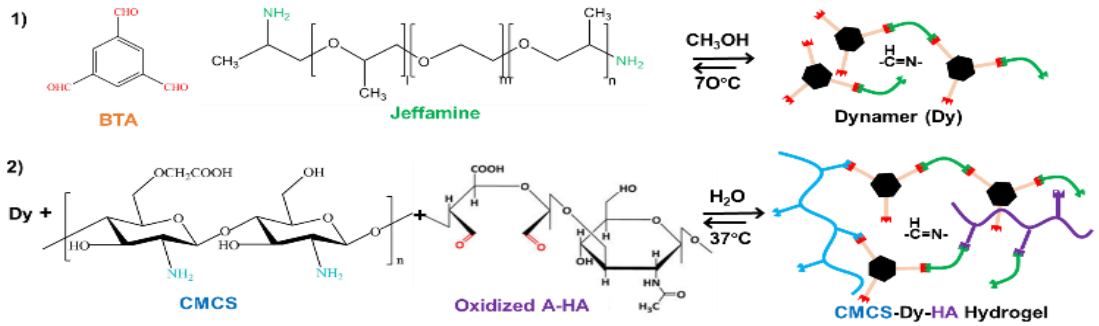
Novel dynamic hydrogels by dual crosslinking of modified biopolymers for sustained drug release in cancer treatment



Scheme 1. Synthesis of dynamic hydrogels by dual imine bonding: 1) reaction of BTA with di-amino Jeffamine to yield a dynamer (Dy), 2) reaction of Dy with CMCS and A-HA to yield a hydrogel.

Controlled drug delivery systems such as nanoparticles, micelles, liposomes, and hydrogels have attracted growing interest in the treatment of cancers [1]. These various systems present many advantages as compared to conventional drug administration routes, including prolonged drug release, constant drug concentration, reduced side effects, protection of drugs from degradation, etc. Among them, hydrogels appear most interesting for sustained delivery of hydrophilic drugs due to their excellent biocompatibility and high water uptaking capacity [2].

This project aims to develop a novel hydrogel from modified biopolymers by dual crosslinking via Schiff-base and genipin reactions. Genipin is a natural crosslinker widely used to crosslink amino-containing biopolymers such as gelatin and chitosan to prepare hydrogels with minimal cytotoxicity, but the gelation is rather slow [3]. In this project, hydrogels will be prepared from aqueous solutions of carboxymethyl chitosan (CMCS), oxidized hyaluronic acid (OHA), genipin and a triamino Jeffamine. A first network will be rapidly formed by Schiff-base reaction between the amino groups of CMCS and Jeffamine with the aldehyde groups of OHA [4]. A second network will be formed progressively by reaction of genipin with the remaining amino groups of CMCS and Jeffamine, thus improving the mechanical properties. In the dual network, Jeffamine serves as a trifunctional core to ensure optimal 3D crosslinking. The structure, rheological, swelling, and self-healing properties of hydrogels will be determined. The contents in CMCS, OHA, genipin and Jeffamine will be varied to modulate the properties of hydrogels.

The potential of hydrogels as drug carrier in cancer treatment will be evaluated by encapsulation of as hydrophilic antitumor drugs such as thymopentin (TP-5), 5-fluorouracil (5-FU) or doxorubicin (DOX). *In vitro* drug release will be studied in pH=7.4 phosphate buffered saline (PBS) at 37°C. Quantitative determination of released drug will be performed using UV or HPLC measurements. The biocompatibility and antitumor efficacy of hydrogels will be evaluated by MTT assay.

References

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[4] R. Yu, Y. Zhang, M. Barboiu, M. Maumus, D. Noël, C. Jorgensen, S. Li, Biobased pH-responsive and self-healing hydrogels prepared from *O*-carboxymethyl chitosan and a 3-dimensional dynamer as cartilage engineering scaffold, Carbohydr. Polym., 244 (2020) 116471.