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Novel biobased hydrogels prepared from O-carboxymethyl chitosan and Jeffamine by dynamic covalent chemistry for biomedical applications

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Hydrogels are a three-dimensional (3D) network of hydrophilic polymers with the ability to absorb large amounts of water or biological fluids without dissolving or losing their structural integrity [1]. This 3D network is formed by crosslinking polymer chains via covalent bonds (chemical hydrogel), or noncovalent bonds such as hydrogen, ionic or hydrophobic bonds (physical hydrogel). The presence of hydrophilic groups such as hydroxyl, carboxyl, amine, amide or sulfonic groups, endows hydrogels with excellent water absorption capacity [2]. Some “smart” hydrogels are able to respond to external stimuli, including pH, temperature, ions, light, etc. [3]. The porous and interconnected structure of hydrogels allows the diffusion of bioactive molecules in the network [1]. In general, hydrogels present physical characteristics similar to native extracellular matrix (ECM) or living tissue, which makes them a material of choice for biomedical applications in drug delivery, wound dressing and tissue engineering [2].

Hydrogels can be obtained from synthetic polymers such as poly(vinyl alcohol), poly(2-hydroxyethyl methacrylate) and poly(ethylene glycol) diacrylate, and biopolymers such as polysaccharides (alginate, chitosan, cellulose, hyaluronic acid), and proteins (gelatin, fibrin, collagen) [4, 5]. Biopolymer based hydrogels exhibit outstanding biocompatibility and biodegradability, and are most promising for applications in the biomedical and pharmaceutical fields [6]. Among the various biopolymers, chitosan has received much attention for the conception of biomaterials because of its outstanding antibacterial properties [7]. However, chitosan is insoluble in aqueous media at neutral or alkaline pH because of strong inter- and intramolecular hydrogen bonding, which greatly limits its potential applications. Chitosan possesses numerous functional amino groups, as well as primary and secondary hydroxyl groups along the polymer chains, which allows chemical modification under mild reaction conditions. Many water-soluble derivatives have been prepared by introducing hydrophilic groups or by grafting a water-soluble polymer on the macromolecular

chain [8]. Among them, carboxymethyl chitosan (CMCS) has attracted wide interest because of its low-cost, ease of synthesis, and high water solubility [9]. CMCS has been widely used for the preparation of hydrogels through physical approaches such as hydrogen bonding, freeze-thawing, and ionotropic gelation, or via chemical approaches such as grafting, free-radical polymerization, enzymatic reaction and condensation reaction.

In this work, a series of dynamic hydrogels were synthesized from CMCS and Jeffamine using benzene-1,3,5-tricarbaldehyde (BTA) as crosslinker. BTA first reacted with Jeffamine to yield a water soluble dynamer (Dy), followed by mixing with CMCS in water to yield a dynamic hydrogel, both based on Schiff-base reaction (Fig. 1). The as-prepared hydrogels were characterized by NMR, FT-IR, SEM and rheology. The effects of CMCS/Dy molar ratio, Jeffamine molar mass, and CMCS molar mass on the physico-chemical properties of hydrogels were investigated. The hydrogels exhibit extraordinary self-healing performance, pH dependent swelling behavior, and outstanding rheological properties. Human mesenchymal stem cells loaded inside hydrogels showed excellent cell viability (Fig. 2), demonstrating the great potential of these hydrogels in cartilage engineering [10]. Therefore, this study offers a new strategy to prepare bioactive dynamic hydrogels for various biomedical applications.

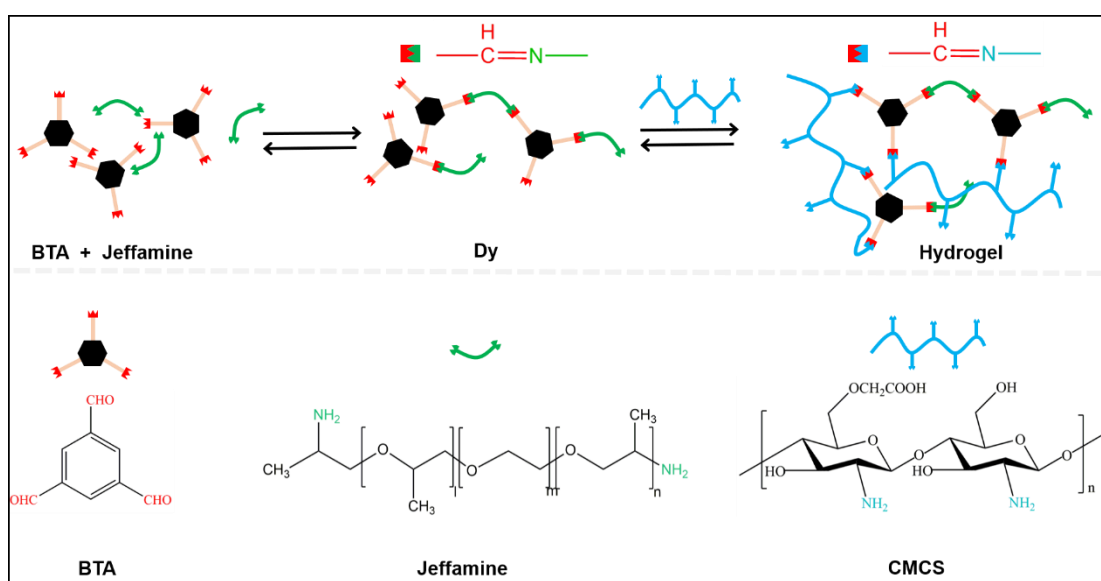


Fig. 1. Synthesis route of CMCS based dynamic hydrogel by Schiff base reaction in 2 steps: 1) reaction between equimolar Jeffamine and BTA to yield a dynamer (Dy), and 2) reaction between Dy and CMCS to yield a hydrogel network.

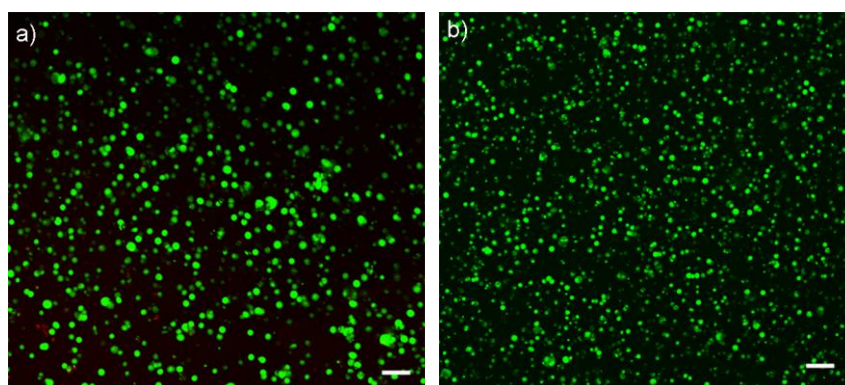


Figure 4. Confocal microscopy images of cells encapsulated in Gel4-1 after 1 day (a) and 7 days (b) culture (viable cells were labelled in green and dead cells in red, scale bar 1 μ m).

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