3D BIO-PRINTABLE MULTI-RESPONSIVE TRIPLE-CROSS-LINKED ALGINATE-BASED INJECTABLE HYDROGELS

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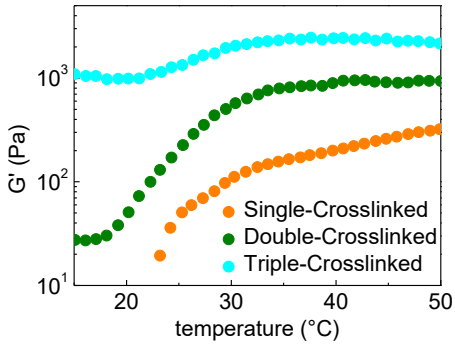
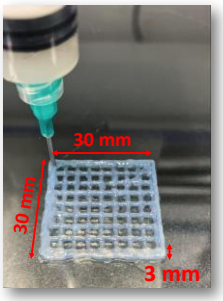
ABSTRACT

In this study we present our late results in shear-thinning, self-healable, pH/thermo-responsive sodium alginate-based hydrogels. A graft copolymer of sodium-alginate bearing thermo-responsive side chains of poly(N-isopropylacrylamide), enriched with the hydrophobic comonomer N- tertiary-butyl-acrylamide (NtBAM) to easily tune the sol-to-gel transition temperature, [NaALG-g-P(NIPAM-co-NtBAM)] was used as the polymer gelator[1]. Endowing the network with additional boronic acid conjugations and/or Ca^{2+} cations we introduce a novel triple-crosslinked gelator, responsive to shear, glycose, pH and temperature. First, the [NaALG-g-P(NIPAM-co-NtBAM)] gelator in the presence of calcium divalent cations, of low f=[Ca^{2+}]/[COO^-]=0.03, forms a weak 3D-network at room temperature due to the ionic interactions with the carboxyl moieties of the sodium alginate. Upon heating, the storage modulus (G') is increased due to a second hydrophobic crosslinking of the thermo-responsive side chains occurs leading to stronger gel formation above T=20 ºC. The existence of the Ca^{2+} ions contribute to a weak-to-strong gel behaviour compared to the calcium-free hydrogel where a sol-to-gel transition is observed (A). The [NaALG-g-P(NIPAM-co-NtBAM)]/Ca^{2+} system was further functionalized with boronic acid. In this approach a strong gel is formed at physiological pH and at low temperature as the network is reinforced by a third dynamic covalent crosslinker (boronate ester bonds). At physiological temperature the network elasticity is significantly escalated through the additional hydrophobic association of the P[NIPAM-co-NtBAM] stickers (A). The triple all-dynamic crosslinking network provides injectability and high life-time integrity (low erosion rate), demonstrating a great potential use in 3D bioprinting as bio-inks (B). Importantly, the properties of this systems can be tailored simply by altering the quantity of the crosslinking agents, rendering it as promising potential candidate for injectable bio-applications (cell transplantation/tissue regeneration etc.)



[A]



[B]

KEYWORDS: Alginate, P(N-isopropylacrylamide-co-N-*tert*-butylacrylamide), Divalent Cations, Boronic Acid Conjugations, Triple Cross-linking

REFERENCES

[1] Safakas, K, Saravanou, S.-F., Iatridi, Z. & Tsitsilianis, C. (2021) *Int. J. Mol. Sci.* 22: 3824