Cross-linked Hyaluronic Acid

Substitution positions of BDDE on HA by NMR and MS

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To increase the in vivo duration of hyaluronic acid (HA) the polysaccharides are often chemically cross-linked by covalent linkage to shorter cross-linker molecules. One of the most common cross-linkers is 1,4-butanediol diglycidyl ether (BDDE). Under alkaline conditions BDDE form ether bonds with the hydroxyls of HA. The cross-linked network thus formed will have different properties depending on the efficiendy of the cross-linking process. Parameters which describe the cross-linked network are therefore important to understand the differences in properties. One important parameter that describe such a network is the degree of cross-linking which combines the degree of modification and the effective cross-linker ratio.[1] Another parameter that might influence the physical properties of the hydrogel is the substitution position of the cross-linker on the polysaccharide. Using NMR spectroscopy and LC-MS/MS, we determined the substitution pattern in hyaluronic acid (HA) hydrogels cross-linked with BDDE. Enzymatic degradation and chromatografic separation was used to create smaller fragments.. Structural analysis of the fragments demonstrated that all four hydroxyl groups of the HA repeating disaccharide could be substituted by BDDE.[2]

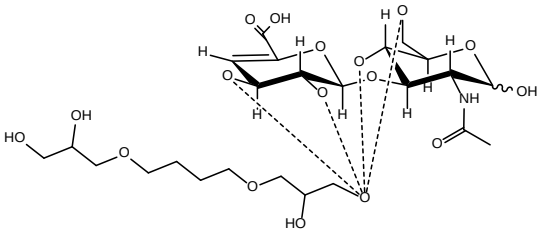

Figure 1. There are four possible substitution positions on each hyaluronic acid disaccharide

[1] L. Kenne et al. *Carbohydr. Polym.* **2013**, *91*, 410-418
[2] F. J. Wende et al. *Carbohydr. Polym.* **2016**, *136*, 1348-1357